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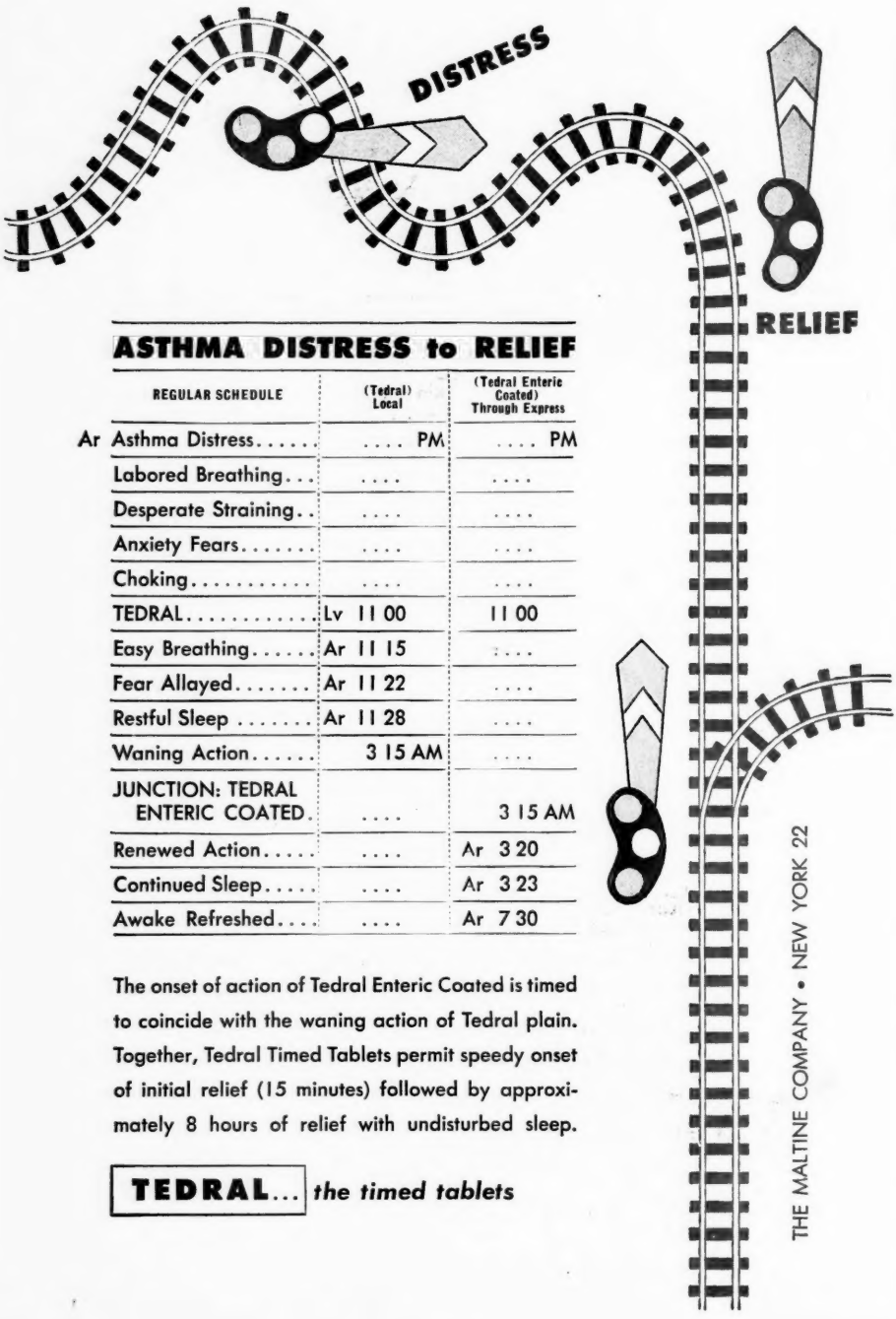

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BACTERIAL ALLERGY

M. SCHERAGO, B.S., D.V.M.
Lexington, Kentucky

THERE appears to be much confusion as to the implications of the term "bacterial allergy." Some use it only in connection with the relationship of bacteria to that group of allergic conditions designated by Coca as atopy. Others associate the term only with those types of hypersensitiveness that result from bacterial infection. Still others use it in the generic sense to include all types of hypersensitive reactions that may develop when the tissues are brought in contact with bacteria or their products or extracts of the organisms. It is in this generic sense that the term bacterial allergy will be employed in this discussion. The types of hypersensitiveness to be treated have been designated: (1) bacterial anaphylaxis (including toxin hypersensitiveness), (2) bacterial atopy, (3) tuberculin-type hypersensitiveness, (4) the Shwartzman reaction, and (5) bacterial heterophile toxicity.

BACTERIAL ANAPHYLAXIS

Any substance that has been proved to be antigenic by its ability to stimulate the production of antibodies will, when injected into an animal, cause it to develop, after a suitable period of incubation, a state of hypersensitiveness which is known as anaphylaxis. An injection of the same antigen any time following the termination of the incubation period (shocking dose) will precipitate the train of symptoms which characterizes anaphylactic shock.

These symptoms vary according to the species of animal, and the method by which the antigen is administered, but not with the type of antigen. In all species of animals, however, there is a subnormal temperature and a fall in blood pressure, and the most striking symptoms are

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From the Department of Bacteriology, University of Kentucky.
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due to the effects upon the smooth muscles. In guinea pigs there is extreme respiratory embarrassment due to the contraction of the abundant supply of smooth muscles in the bronchioles. The animals develop nasal and bronchial changes similar to those seen in human beings with asthma and vasomotor rhinitis. Death is due to suffocation. Rabbits do not show marked symptoms, as a rule, except those of collapse. Death is due to heart failure. The muscles of the pulmonary arteries cause constriction of these vessels, with blocking of the pulmonary circulation. The right side of the heart is dilated by the back pressure. The dog shows symptoms of restlessness, diarrhea and vomiting, followed by epileptiform seizures, coma and death. The liver and intestines are congested. Cattle show uneasiness, labored breathing, edematous swellings around the eyes, udder, anus, and vulva, and diarrhea. They seldom, if ever, die as the result of the shock. Monkeys are not easily sensitized, which suggests that man probably is not easily rendered anaphylactic; as is borne out by clinical experience. Indeed, it is doubtful if anaphylaxis, as it occurs in animals, ever occurs in man. Those crises in man that are similar in clinical appearance to anaphylactic shock may be the result of a somewhat different mechanism. While different animal species react with entirely different trains of symptoms, for each species the symptoms of anaphylactic shock are the same, no matter what antigen is involved.

The anaphylactic state may be passively transmitted to normal animals by transfusing them with blood or serum from a hypersensitive animal. An animal thus passively sensitized will give the anaphylactic reactions if, a few hours after the transfusion, it is given an injection of the antigen to which the donating animal was sensitized. This indicates that an anaphylactic antibody is present in the blood of the actively sensitized animal.

Another method of recognizing the presence of the anaphylactic state is the one devised by Dale. A piece of smooth muscle such as a strip of the uterus from a sensitized virgin female guinea pig is immersed in Ringer's solution kept at 37° C., and one end is connected with a kymograph needle. Upon the addition of a small quantity of the specific antigen to the solution, characteristic contractions of the uterus will be recorded on the kymograph drum. The sensitivity of the excised muscle reveals that the anaphylactic antibody is not confined to the blood stream, but is present in the tissues as well.

The anaphylactic reaction is specific. As in other immunological reactions, the specificity of a complex antigen, e.g., lipo-protein, is influenced by the hapten (nonprotein) portion of the antigen. Here too, the hapten alone will react with the antibodies produced by the injection of the complex antigen, but will not cause the production of antibodies. In an animal sensitized by such an antigenic complex, the hapten alone will elicit shock and the Dale reaction (smooth muscle contraction), although it cannot sensitize an animal. Thus, haptens assume the same role in anaphylaxis as they do in other immune reactions.

Animals in the anaphylactic state are also skin sensitive. An intracutaneous injection of the specific antigen is followed within a few minutes by a local reaction of edema and erythema which shortly disappears.

If repeated subcutaneous injections of antigen are given a rabbit at intervals of several days, not only will the anaphylactic state become established, but, in addition, the capacity of the tissues to react locally at any site at which the antigen is injected becomes greatly intensified. The initial reaction of edema and erythema persists and increases in size and intensity until in the course of about two days, hemorrhage and necrosis appear, with the formation of a sterile abscess at the site of injection. This is the Arthus reaction. Specific precipitin is demonstrable in the serum of the animal and the capacity to react locally in the Arthus manner is passively transferable to a normal animal by the injection of serum from the hypersensitive one.

Although the amount of antigen required to elicit the Arthus reaction is greater than that required for the usual local anaphylactic type, no amount of the antigen will produce the Arthus reaction in an animal that is only in the anaphylactic state. Some regard the Arthus reaction, therefore, as a manifestation of a higher degree of anaphylactic sensitivity.

In man an Arthus-like reaction may occur in the course of rabies vaccination. It appears in the form of indurated areas at the sites of inoculation after the sixth or seventh injection of the vaccine.

Animals that recover from an anaphylactic shock are desensitized and remain so for a considerable length of time. It is possible to forestall the development of the anaphylactic state by injecting large doses of the antigen during the later days of the incubation period, in which case desensitization occurs without the appearance of shock. Animals may also be desensitized, without the production of shock, by the administration of the antigen in multiple small doses over a considerable period of time.

That bacteria are capable of producing anaphylaxis was first demonstrated by Rosenau and Anderson (1907) who sensitized guinea pigs with subcutaneous injections of extracts of colon, tubercle, anthrax, and typhoid bacilli. Kraus and Doerr (1908) then proved that bacterial anaphylaxis was passively transferable by showing that guinea pigs which were injected with the sera from guinea pigs that had been sensisitized to typhoid and cholera organisms, respectively, became sensitized to the homologous organisms. Later, Zinsser and Parker (1917) demonstrated by the Dale test that uterine strips from young guinea pigs passively sensitized with antityphoid serum from a rabbit gave typical contractions when extracts of typhoid bacilli were added to the bath. Gay and Claypole (1914) found that typhoid immune rabbits were skin sensitive to typhoidin and that the sensitivity was passively transferable. Julianelle (1930) also showed that rabbits which received intracutaneous injections of heat killed pneumococci became skin sensitive to pneumococ-

cus nucleoprotein, and that the sensitivity was passively transferable. The sensitivity to bacterial haptens of animals anaphylactically sensitized to bacteria was demonstrated by Enders (1929), Morris (1936) and others. Enders elicited typical anaphylactic reactions with tubercle bacillus carbohydrate in guinea pigs passively sensitized with antitubercle bacillus rabbit serum. Morris obtained anaphylactic reactions with the polysaccharide of the Friedlander bacillus in animals that were injected with a Friedlander bacillus antiserum. Morris also completely desensitized the animals with injections of the polysaccharide of the organisms. Thus, all of the analogies with nonbacterial anaphylaxis (shock, passive transfer, uterine sensitivity, skin sensitivity, sensitivity to specific haptens, and specific desensitization) have been fulfilled with bacterial materials.

Other organisms, in addition to those already referred to, whose extracts have been found to be capable of sensitizing guinea pigs are *Bacillus subtilis, Brucella abortus, Malleomyces mallei, Neisseria intracellularis, Neisseriae gonorrheae, Treponema pallida,* and, incidentally, yeasts. It will be noted that among the organisms found capable of inducing anaphylactic shock are two nonpathogenic species of bacteria, one a commensal *(E. coli)* and the other a saphrophyte *(B. subtilis),* as well as yeasts (also nonpathogenic).

Typical anaphylactic reactions have also been produced in guinea pigs actively sensitized with diphtheria toxin and toxoid, and in those passively sensitized with antitoxic sera derived either from guinea pigs or from human beings. To prove that the hypersensitiveness was due to the toxin itself and not to any other bacterial product in the filtrate, Neill and Fleming (1929) removed all detectable traces of other antibodies without removal of the antitoxic antibodies by absorbing diphtheria antitoxic sera with heavy suspensions of the diphtheria bacilli, and used the absorbed antisera for passive sensitization experiments. The absorption removed from the antisera all precipitins and all capacity for passive sensitization against nucleoprotein solutions. They concluded that the animals which became passively sensitized with the absorbed antiserum could have been sensitized only to the toxin in the toxic filtrate.

BACTERIAL ATOPY

The term atopy, introduced by Coca, differentiates those hypersensitive reactions occurring in man, in which antibody-like substances (reagins) are present but in which only local passive transfer is possible, and then only from man to man. Atopy has many of the characteristics of anaphylaxis—the dependence upon an antibody-like mediating substance (reagin); the immediate local response to intracutaneous injection of the allergen (atopen), with edema and erythema of short duration; the respiratory symptoms; the capacity for desensitization; and the passive transfer of skin sensitivity (the Prausnitz-Küstner reaction). It differs from anaphylaxis in the nature of the mediating substance, the absence of demonstrable specific precipitins, the tendency for certain tissues to be-

come sensitized, the influence of heredity, the spontaneous occurrence, the susceptibility of only the skin to passive transfer, and the absence, usually, of violent reactions and death.

The relation of bacterial infection to asthma and other manifestations of atopic hypersensitiveness in man has been the subject of much controversy. Many allergists are unwilling to accept hypersensitiveness to infecting bacteria as an explanation of such conditions as asthma and hay fever because the skin reactions obtained with bacterial products are of the delayed and inflammatory nature instead of the immediate urticarial type obtained with simple protein extracts. They also point to the fact that treatment with vaccines rarely produces general reactions with urticaria and coryza. Others, on the other hand, hold that when the patient has one or two attacks of asthma during the year, although there has been no change in his environment, occupation and diet, and when the attacks are definitely associated with an accute respiratory infection, it is reasonable to make the diagnosis of "bacterial asthma" and to assume that the bronchial spasm is dependent upon the infection. They believe that a hypersensitiveness to the infecting bacteria and their products, alone and without the intervention of other foreign proteins, may result in allergic symptoms; that respiratory infections alone can cause asthma; and that acute and chronic infections can produce urticaria.

There are other ways in which bacterial infections can influence allergy.

1. The resistance of the body to the entrance of foreign substances is lowered during infections. Hence it is not unusual for a hypersensitive reaction to originate in association with an infection.

2. In patients who are already hypersensitive, mild infections, such as colds, can precipitate the manifestations of allergy, by lowering the threshold so as to make a slight contact with foreign substances adequate to produce symptoms.

3. In severe febrile infections, the allergic symptoms will diasppear due, probably, to a nonspecific effect.

4. Infections may complicate an original simple condition.

The role of nonpathogenic bacteria in atopy is not too clear. Considering the ubiquity of these microorganisms, the constant exposure of the skin and the mucus membranes to them, and the minuteness of the dose of allergen that will elicit such allergic reactions as hay fever, it would not appear unreasonable to suspect them of being associated with atopic conditions. Closely related microorganisms, the molds, have been proved to be associated with various types of allergic conditions in man, and nonpathogenic bacteria, commensals *(E. coli)* as well as saprophytes *(B. subtilis)*, are antigenic, and have been proved to be capable of inciting hypersensitiveness of the anaphylactic type when injected into guinea pigs. Weil (1946), in a recent editorial, has stated that "there is no basic reason why persons of the necessary constitutional make-up should not react

vehemently to bacterial antigens. In the case of asthma this is quite widely and naïvely accepted to be the case" although "there is no proof"—"not because there is nothing to be proved but because we really have made no systematic effort to prove or disprove." Weil has laid down the gauntlet to the bacteriologist stating, "Only by putting to use the painstaking methods of modern bacteriology, will we be able to replace notions by exact information. And this information will be necessary before we can state with any degree of confidence whether or not microbial antigens are involved in a given manifestation of allergy."

TUBERCULIN-TYPE HYPERSENSITIVENESS

The two types of hypersensitiveness discussed thus far may occur whether the organisms involved are pathogenic or not. A third type of reaction, because it occurs only in the infected individual, is variously referred to as bacterial hypersensitiveness, infection hypersensitiveness, infection allergy or tuberculin-type hypersensitiveness.

Of these terms, tuberculin-type hypersensitiveness has been chosen for use in this discussion because it expresses more accurately the type of reaction to be dealt with. The other types of hypersensitiveness can also occur as a result of infection, consequently the term infection hypersensitiveness or infection allergy could, with equal propriety, be applied to the other types of allergy if the offending agent happened to be of infectious origin.

When pathogenic bacteria, living or dead, or their products are introduced into the tissues, the effects produced differ in different species and with different organisms. If, for example, living organisms of the toxigenic group such as *Corynebacterium diphtheriae* or *Clostridium tetani* are introduced, infection will result. If the tissues can produce enough antitoxin to neutralize the toxin, recovery will take place and antitoxic immunity will be established. The existence of this type of immunity is detectable by skin tests such as the Shick or the Dick tests, or by the ability of the individual to withstand with impunity injections of the causative organism or its toxin. The immunity may exist for a considerable or indefinite period of time following the disappearance of the infection.

Infection with such organisms as *Mycobacterium tuberculosis,* streptococci, *Diplococcus pneumoniae* or some members of the *Enterobacteriaceae* may also result in the formation of circulating antibodies. These antibodies may be utilized to demonstrate the presence of infection by immunological or serological methods (complement fixation tests, agglutination tests, et cetera). In addition, however, after the infection has been established, the injection of either the organisms themselves or their products, instead of producing no reaction at all or of stimulating antibody production (as would occur upon injection into a normal control), is followed by an abnormal delayed type of reaction, usually occurring within twenty-four hours. This is typified by the reactions that are induced in the tuberculous

guinea pig upon the injection of tuberculin (tuberculoprotein). If the injection is made intracutaneously, there appears in from eight to forty-eight hours a local reaction consisting of an area of edema and erythema, 1 to 2 cm. in diameter, with a central area of necrosis, the intensity of the reaction varying with the dose and potency of the tuberculin, and the hypersensitive state of the animal. The reaction gradually subsides, and fades after seventy-two hours. Microscopic examination of an excised reacting area reveals capillary dilatation, general congestion, some fibrin, and a large number of polymorphonuclear and mononuclear leucocytes.

The subcutaneous injection of tuberculin into a tuberculous animal is followed by three types of reaction: a local reaction at the site of injection, characterized by the classical symptoms of inflammation; a focal reaction about the tuberculous process, the severity depending upon the dose of tuberculin injected, but usually consisting of edema, congestion and hemorrhage; and a general reaction marked by symptoms of fever, chills, rapid pulse, malaise, anorexia, and prostration, and terminating in death.

The tuberculin-type hypersensitiveness differs from bacterial anaphylaxis and from bacterial atopy in several ways.

1. When the infecting agent, or its soluble protein is injected into the skin of the sensitized body, instead of causing a prompt wheal and erythema which disappears in a few hours, as in the simple anaphylactic or atopic reaction, (or which progresses to necrosis as in the Arthus reaction), there occurs a delayed inflammatory reaction which begins to appear only after some hours, and then progresses to reach a maximum size and intensity within twenty-four to forty-eight hours, after which it slowly fades.

2. The local reaction is characterized macroscopically by erythema, and by indurated swelling that contrasts with the soft, edematous, swelling of the anaphylactic or atopic reaction. In the more intense reactions, necrosis and sloughing of the skin occur.

3. The tuberculin-type hypersensitiveness cannot be transferred to a normal individual by the injection of serum from a hypersensitive one.

4. The cells of the body with tuberculin-type hypersensitiveness which have so far been tested (spleen, blood leukocytes, bone marrow) are killed in vitro by contact with the specific bacterial protein, whereas such cells from the body with anaphylactic, Arthus, or atopic type of hypersensitiveness are not killed in vitro by contact with the specific agent.

The tuberculin-type hypersensitiveness differs from bacterial anaphylaxis also in the following respects:

1. When the antigen is injected into an animal subcutaneously or intravascularly, the animal may become severely ill, or may die; but instead of the prompt, sudden collapse that is characteristic of anaphylactic shock, the symptoms appear only after a lapse of some hours and increase gradually in intensity, and if death occurs it is usually not before eighteen

to twenty-four hours. At any site in the body at which there is a focus of infection caused by the specific microorganism, inflammation, necrosis, and hemorrhage may occur (the so-called "focal reaction").

2. Whereas almost any soluble protein will induce the anaphylactic type of hypersensitiveness, for the establishment of the tuberculin type, parenteral contact with living or dead bacteria or filterable viruses is ordinarily necessary. The soluble proteins of the bacteria will readily elicit the tuberculin-type reaction once this form of hypersensitiveness has been established.

3. Neither carbohydrates nor lipids (haptens) have been shown to be capable of eliciting the tuberculin-type reaction in the hypersensitive body.

4. In contrast to anaphylactic hypersensitiveness, in which sensitivity appears to be limited to involuntary muscle, vascular endothelium and, possibly, certain glandular cells, there is a more widespread sensitivity of the body cells in tuberculin-type hypersensitiveness.

5. The sensitivity of excised smooth muscle (the Dale reaction) is not demonstrable in tuberculin-type hypersensitiveness.

With regard to the mechanism of the tuberculin-type hypersensitiveness, there is ample evidence that the sensitizing antigen is derived from the bacterial cells and is highly specific, that toxins or other unstable bacterial antigens are not involved, and that inflammatory cellular reactions are essential in its development. No antibodies or antibody-like substances akin to reagin that would account for the hypersensitiveness have been demonstrated in individuals with the tuberculin type. Nevertheless, Rich (1944) is strongly of the opinion that antibodies are produced and are involved in the mechanism of this type of hypersensitiveness. He reasons that the fact that the antibody is not present in the blood in amounts sufficient to permit passive transfer is not convincing proof that tuberculin hypersensitiveness is not determined by antibody, for, he points out, even in anaphylactic hypersensitivity, in which sensitizing antibody is readily demonstrable in the serum, the circulating increment of antibody is an excess which is entirely unnecessary for the hypersensitive reaction. Even in anaphylaxis the effective antibody is that portion which is intimately associated with the cells. If hypersensitive tissues of the anaphylactic animal (uterine muscle) are perfused until the circulating fluid contains no more detectable antibody, they still react anaphylactically in vitro on contact with the antigen. Furthermore, anaphylactic hypersensitivity persists in the intact body after the animal's blood has been replaced by normal blood.

It is possible, therefore, that the conditions governing the development of tuberculin-type hypersensitiveness may be such that a sufficient amount of antibody is produced to sensitize the tissues, but not enough to accumulate in the circulation in an excess amount sufficient to detect with any regularity in passive transfers. Attempts have been made to extract sensitizing antibody from the tissues of the tuberculous body, but the

results have been irregular and far from satisfying, although some investigators, including Rich, have reported that they have had rare, suggestively successful results. Recently, Chase (1945) succeeded in producing, in normal guinea pigs, a transient cutaneous hypersensitiveness to tuberculin that exhibited the essential features of the typical tuberculin reaction, by injecting them with cells secured from the peritoneal exudates, or spleens, or lymph nodes of tuberculin sensitive guinea pigs.

In further support of the antibody concept, Rich points to five additional observations, as follows:

1. The high degree of the specificity of the hypersensitiveness. Tuberculin-type hypersensitiveness may become established during infection with most if not all microorganisms, and when it is established, the body will react characteristically and in a highly specific way to the protein of the particular infecting microorganism.

2. The anamnestic reaction. When a specific antibody has once been produced as a result of contact of the tissues with a foreign antigen, the amount of antibody demonstrable in the circulation gradually decreases with the passing of time if there is no further contact with the same antigen, until, at length, none at all can be detected. If now the antigen enters the tissues again, antibody will reappear in the circulation, and will reach a given level in a much shorter time than was required following the first contact with the antigen. It is significant, therefore, that this anamnestic effect that is so characteristic of antibody development in general, is also a characteristic of tuberculin-type hypersensitivity. Following a well-resisted tuberculous infection in animals and in man, hypersensitivity often wanes, and after several years it may decline to so low a level that large doses of tuberculin will fail to produce a reaction. If, now, re-infection occurs, hypersensitivity will reappear in a shorter time than was required for its establishment following the first infection.

3. The condition present in the white rat. This animal is a poor antibody producer and, similarly, exhibits little tendency to develop the anaphylactic type of hypersensitiveness which is dependent upon antibody. The rat displays the same refractoriness to the development of tuberculin-type hypersensitiveness following infection with the tubercle bacillus as it does to the development of anaphylaxis.

4. The phenomenon of specific desensitization. As in anaphylaxis, so too in tuberculin-type hypersensitiveness, the hypersensitiveness can be depressed or abolished by desensitization; and by the same desensitization procedures (injection of a single large dose, or of repeated, increasing doses of the specific protein).

5. Enhancement of hypersensitiveness. A procedure (suspension of the bacilli in paraffin oil before injection) that is known to enhance markedly the production of antibodies to the tubercle bacillus, also enhances markedly the degree of hypersensitivity.

Rich concludes that it seems highly probable that tuberculin-type hypersensitiveness is dependent upon antibody, but that in contrast to other types practically all of the antibody is closely associated with the cells, and too little excess antibody accumulates in the circulation to permit passive transfer. He concedes, however, that it is possible that an acquired capacity to react specifically to a foreign protein may be effected through some as yet undefined and undiscovered mechanism that is entirely independent of antibody.

In a number of infectious diseases, the development of the tuberculin-type hypersensitiveness is utilized in a practical way for diagnostic purposes. For example, to detect the presence of tuberculous infection, individuals may be tested for hypersensitiveness to tuberculin. The testing may be done by von Pirquet's cutaneous method, in which the tuberculin is rubbed on to the scarified skin; Moro's percutaneous method, in which the tuberculin is incorporated in an ointment and rubbed into the skin; Mantoux's method, in which the tuberculin is injected intracutaneously; Calmette's ophthalmic method, in which the tuberculin is dropped into the conjunctiva; Koch's original method, in which the tuberculin is injected subcutaneously; or Vollmer and Goldberger's patch test, in which a thin filter paper, impregnated with tuberculin and then dried, is applied to the skin. In all of the skin tests, a positive reaction consists in the appearance, after forty-eight hours, of edema and redness of varying degrees. In the ophthalmic test, which is used only in lower animals, a positive reaction consists of a conjunctivitis during the course of which pus is formed and appears at the inner canthus. In the subcutaneous test, a positive reaction consists of a rise in temperature of at least 2° F., which appears some time between the eighth and eighteenth hours following the injection and subsides within twenty-four hours. This test has not been used in human beings, and even in the lower animals it has been largely replaced by the intradermal tests.

Other infectious diseases in which the test for tuberculin-type hypersensitiveness has been employed for diagnostic purposes are: glanders of horses, using mallein; contagious abortion of cattle, using abortin; brucellosis, using brucellin; para-tuberculosis of cattle, using johnin; and syphilis, using luetin. Intradermal tests have also been described for gonoccocal and meningoccal infections, typhoid fever, tularemia, rhinoscleroma, soft chancre, actimomycosis, typhus fever, and pullorum disease in chickens, as well as for certain parasitic infections.

In virus diseases, a similar type of hypersensitiveness has been observed. The characteristic response to reinoculation with vaccinia virus is one of the classical examples. If a person who has been successfully vaccinated is again injected with the vaccine during the period of decreasing immunity, but before he has again become fully susceptible, the papules appear earlier (sometimes within twenty-four hours), and vesiculation and pustulation, when they occur, appear much earlier than after pri-

mary vaccination. Very frequently, however, the reaction ceases at the papular stage, and even this may be so transitory as to be missed unless daily examinations are made. There is usually much less induration around the papules or vesicles after a secondary than after a primary vaccination, and the constitutional symptoms are milder. In other words, there is the typical hypersensitiveness combination of accelerated response with localization of infection. Vaccinia virus killed by heating to high temperatures is capable of producing the characteristic early reaction with papule formation in persons previously vaccinated; while it has no effect in unvaccinated persons, nor does it produce an active immunity. Desensitization of individuals who exhibit the hypersensitiveness to vaccinal protein may be accomplished by repeated injections of killed virus.

Among the theories that have been advanced to explain the etiology of postvaccinal encephalitis is the hypersensitiveness one. It is thought that hypersensitiveness is the primary factor in causing the thrombosis which produces the characteristic histological picture of demyelination in this condition.

On the experimental side, Force and Beckwith (1915) introduced a laboratory test for the diagnosis of smallpox, which depended upon hypersensitiveness reactions. They sensitized rabbits by inoculating them with vaccinia and later inoculated them with the contents of smallpox vessicles. The animals developed a severe intradermal reaction in twenty-four to forty-eight hours. Blaxall (1923) obtained similar results, even with boiled variolar antigen and Thompson (1930) found that the hypersensitiveness could be passively transferred by injection of serum. Dienes and Naterman (1937) found that the skin reactions also developed in guinea pigs on revaccination. The reactions were of the "delayed type," and were characterized, microscopically, by infiltration with large mononuclear leucocytes.

Patients with lymphogranuloma inguinale, a venereal disease caused by a virus, are hypersensitive to sterilized pus from the bubos, and develop the usual skin reaction within twenty-four hours, when the material is injected intradermally. This is the Frei diagnostic test. The skin hypersensitiveness develops quite early in the disease and persists for a long period after recovery. Upon intravenous injection, the antigen gives rise to a febrile response. Antigens have also been prepared from infected mouse brain and, more recently, from infected chick embryo. The latter is said to give rise to fewer nonspecific reactions than the mouse brain antigen. Melczer and Sipos (1938) have reported that the hypersensitiveness to the Frei antigen can be transmitted by injections of blood serum, and be demonstrated by the Prausnitz-Kustner technique.

In experimental poliomyelitis, Brebner (1931-2) found that if the virus was injected into the spleen of immune monkeys (either by recovery from infection or by vaccination) sudden death occurred. Death did not result unless about seven weeks had elapsed since the beginning of

immunization, or the onset of the paralytic attack. That such a finding might be due to a hypersensitive reaction was suggested by the post-mortem appearance of hemorrhages in the mucous membranes, necrosis of the liver lobules, and hemorrhages in the medulla. Jungeblut (1931) has also indicated that the altered response of a prolonged febrile disturbance, which develops three to four days after intracerebral injection of virus into monkeys which had been injected parenterally on a number of occasions, is suggestive of a hypersensitive phenomenon.

Another virus disease in which the hypersensitive state has been observed is Virus III infection in rabbits. Andrewes (1928) has reported that rabbits which had been solidly immunized showed a relatively small local lesion when inoculated in the testes, but no nuclear inclusions were present in these lesions. Partially immunized rabbits developed more pronounced testicular lesions, as judged histologically, than did either normal or solidly immunized animals. The lesions, however, unlike those produced in normal rabbits, were usually free from nuclear inclusion bodies.

It is highly probable that detailed studies would reveal the presence of infection hypersensitiveness in other virus infections.

Incidentally, in recent years, another problem in allergy has arisen as a result of the use of virus or rickettsial vaccines prepared by growing the organisms on egg yolk sacs or chick embryos. Individuals who are sensitive to egg or chicken may develop allergic manifestations if they are given vaccines prepared in this manner.

The tuberculin-type hypersensitiveness has been suggested as a possible explanation of some features of rheumatic fever, particularly the joint lesions and the fever, and possibly also the typical Aschoff modules. An attack of streptococcic sore throat often precedes the onset of rheumatic fever. Rheumatic patients are not infrequently hypersensitive to streptococci, and the injection of small doses of dead streptococci will produce in them far more severe reactions than in normal subjects. Swift and his collaborators (1928) induced hypersensitiveness to *Streptococcus viridans* in rabbits which, on subsequent injection of the organisms reacted with extreme edema. Zinsser and his associates (1939) have summarized the premises upon which the hypersensitive view of rheumatism is based as follows:

"1. In acute and subacute rheumatic conditions, the joint fluids are usually sterile, though signs of inflammation are present.

"2. The organisms isolated from rheumatic cases are not bacteriologically or serologically identical.

"3. Streptococcus foci are found in many rheumatic cases.

"4. Joint lesions can be produced in animals with products of these organisms, and such joint hypersusceptibility can be shown to some extent to be parallel with skin allergy."

In scarlet fever, the tuberculin-type hypersensitiveness is also thought to play an important role. In this disease, the evidences of septicemia are due to the invasion by the streptococci themselves, whereas the characteristic symptoms are due to the effects of the soluble exotoxin. This toxin is present in the broth filtrate of cultures of the organism and differs from other exotoxins by not being affected by age. It is toxic only for man; animals and young infants are not affected. Many believe, therefore, that the rash and clinical symptoms may be due to an acquired hypersensitiveness to the products of the organism and that the supposed exotoxin is in reality a nontoxic antigen. Infants at birth are negative to intracutaneous injections of the scarlatinal filtrates and their blood sera possess no neutralizing power. If they later become infected with streptococci, they become sensitized so that a subsequent infection with the same organism gives rise to an allergic reaction which is manifested by the toxic syndrome of scarlet fever.

Infection with pneumococci, or vaccination with dead pneumococci, produces cutaneous hypersensitiveness of the tuberculin type. Animals so sensitized by the intact bacteria give delayed tuberculin-type skin reactions to the injection of intact pneumococci or of the soluble protein. If, on the other hand, the soluble pneumococcal protein is injected repeatedly into a normal animal, a state of hypersensitiveness is established in which the cutaneous reaction produced by the injection of the protein resembles the Arthus reaction, and this hypersensitiveness is passively transferable.

Among the more recent reports of diseases in which tuberculin-type hypersensitiveness is considered to be involved are: (1) different ocular affections, particularly phlyctenular conjunctivitis, attributed by Ré (1944) to hypersensitive reactions to tubercle proteins; (2) erythema nodosum, considered by Sigalov (1944) as usually the expression of early hypersensitiveness to tubercle bacilli, with a local exacerbation of the tuberculous process either preceding or accompanying the eruption, and by Dementiev (1944) as a definite hypersensitive syndrome caused by various diseases but in the majority of his cases by tuberculosis, and (3) periarteritis nodosa, regarded by Wilson and Alexander (1945) as associated in some cases with hypersensitiveness to bacteria.

The popularity of penicillin as a therapeutic agent has given rise to another problem in which the tuberculin-type hypersensitiveness is involved. Rostenberg and Welch (1945), in a study of the types of hypersensitiveness induced by penicillin, found that the incidence of the tuberculin type to crystalline penicillin sodium in a group of 144 persons was 5.5 per cent. None had had prior contact with penicillin. Cormia et al (1945), in a study of 2,000 persons who received penicillin, reported that 0.5 per cent showed reactions so severe that treatment had to be stopped. They suggest that a previous fungus disease may enhance the development

of reactiveness to penicillin, and state that testing with penicillin has been of limited value as an aid in diagnosis and a guide for further treatment.

THE SHWARTZMAN REACTION

Shwartzman (1937) found that if bacterial filtrates, e.g., typhoid, are injected into the skin of normal rabbits and, twelve to twenty-four hours later, the same or different bacterial filtrates are injected intravenously, a severe reaction occurs at the site of the original skin (preparatory) injection. The reaction develops in about four hours after the intravenous (provocative) injection and consists of hemorrhage and necrosis. The skin loses its capacity to react in about forty-eight hours after the preparatory skin injection. A second injection directly into the prepared skin site fails to produce the reaction; the second injection must be made intravascularly. The reaction is not specific, since the filtrate of an entirely different species of bacterium than that used for the preparatory injection may be used for the intravenous injection, and it is not passively transferable. Nonbacterial substances such as egg albumen or horse serum have failed to reproduce the phenomenon. The bacterial filtrates are neutralized by specific immune sera.

The mechanism of the reaction has not been determined. Shwartzman states that it is not a mere trauma, it is not due to the local blockade of reticuloendothelial cells nor merely to increased permeability of the capillaries nor to inflammation, and that it is entirely unrelated to anaphylaxis. He does not believe that the reaction is one of anaphylactic shock because (1) it requires an incubation period of about twelve hours and cannot be elicited after forty-eight hours, while the incubation period for anaphylaxis is about ten days and sensitivity lasts for months or years; (2) there is no specific relationship between the preparatory and provocative factors, as there is in anaphylaxis; (3) it can only be produced by certain bacterial filtrates, while any antigenic substance can elicit anaphylaxis; (4) it cannot be passively transferred while anaphylaxis can; (5) both the preparatory and provocative factors are neutralizable by immune sera, and (6) there is no specific desensitization as there is in anaphylaxis. Shwartzman concludes that his phenomenon deals with a hitherto unrecognized functional disturbance in the susceptibility of the animal tissue which is elicited by certain bacterial active principles and that it displays a mechanism whereby injury may be produced through the synergistic effect of bacteria and their products and also through the concerted effect of bacteria, their products and nonrelated anaphylactic processes.

Black-Schaffer, Kerby and Hiebert (1946) have recently reported that living organisms recovered from a case of purpuric meningococcemia, after two washings in normal salt solution, possessed the ability to prepare the skin of rabbits and elicit the Shwartzman phenomenon upon intravenous injection. When the organisms were heat-killed, they still retained these properties. Contrary to Shwartzman's experience, they found that the washed organisms were even more potent than the supernatant fluid. They

concluded that purpuric meningococcemia suggests a spontaneously occurring Shwartzman reaction, with the organisms present in the purpuric lesions as the probable counterpart of those that were intradermally injected in the rabbit and the meningococcemia as the probable counterpart of the provocative intravenous dose.

HETEROPHILE TOXICITY

Forssman (1911) discovered that the tissues of many species of animals, e.g., guinea pig, horse, cat, possess an antigen which, when injected into an animal whose tissues do not possess it, e.g., rabbit, will cause the animal to produce antibodies that are capable of causing hemolysis of sheep red blood cells. The antigen, because of its apparent heterogeneity, has been called heterophile antigen and the antibody engendered heterophile antibody. The heterophile antiserum of the Forssman type, in addition to other properties, possesses toxicity. When it is injected intravenously into animals whose tissues contain the Forssman antigen, it produces symptoms analogous to anaphylactic shock, the animals dying with postmortem findings of hemorrhage in the lungs, liver, and kidney capsule. When injected intracutaneously, it causes a characteristic local edema and necrosis. A reverse heterophile toxicity may also be produced. If a rabbit which has reacted to injections of heterophile antigen, e.g., sheep red cells, by producing a high-titered heterophile antiserum is later injected with heterophile antigen even from another source, e.g., guinea pig kidney, it will react with symptoms of heterophile toxicity.

It is possible that the mechanism of Forssman heterophile toxicity is the same as that of anaphylaxis. However, heterophile toxicity differs from anaphylaxis in several respects.

1. Intoxication with heterophile antiserum causes more extensive edema and hemorrhage in the lungs.
2. Animals cannot be desensitized to the toxic effects of the antiserum.
3. The uterine muscle of a normal guinea pig fails to contract when exposed to the heterophile antiserum.
4. When injected in the skin of a guinea pig, the heterophile antiserum causes a characteristic local necrosis.
5. The most significant factor in the cause of death in heterophile toxicity is the rapidly increased permeability of endothelial linings and cell membranes.

The Forssman heterophile antigen is found widely distributed in many mammals, birds, fish, and bacteria, and is a primitive biological characteristic not associated with phylogenic development. The bacteria which have been found to possess the heterophile antigen include the pneumococcus, green streptococcus, hemorrhagic septicemia group, *Neiseria catarrhalis, Bacillus anthracis, Shigella dysenteriae, Salmonella paratyphi, Clostridium perfringens, Clostridium oedematiens, Bacillus cereus, Bacillus megartherium, Bacillus petasites,* and *Alcaligenes faecalis.*

It would appear then that antiserums against heterophile-containing bacteria produced in animals (rabbits) which do not possess heterophile antigen would be dangerous to use in animals whose tissues possess Forssman antigen or in human beings belonging to blood groups A and AB (their red cells possess Forssman antigen), whereas similar antiserums produced in animals whose tissues or red cells possess the Forssman antigen could be used with safety in all animals. On the other hand, animals whose tissues do not possess heterophile antigen and human beings belonging to types B and O (possess no Forssman antigen) could develop the heterophile antibody as a result of infection with microorganisms containing the antigen. Such individuals, if later vaccinated with organisms containing heterophile antigen or if given horse serum (contains some heterophile antigen) might react with symptoms of heterophile toxicity, the degree of the reaction depending upon the amount of heterophile immune body present in the individual. This could account for the toxicity of horse serum in some cases.

SUMMARY

Of the five types of bacterial hypersensitiveness which have been discussed, three (anaphylaxis, atopy and heterophile toxicity) do not differ materially from their prototypes to nonbacterial agents. The other two (tuberculin-type and Shwartzman-type) have thus far been induced and elicited only with microorganisms and their products. It is possible that underlying all types of hypersensitiveness is a common basic principle, namely, that the exposure of the tissues to an undigested foreign or abnormal substance stimulates the production of a specific antibody, different for each substance, and that the different forms of hypersensitivity reaction are effects that result from the interaction of antibody and antigen under different conditions.

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THE ASTHMATIC CHILD: A SCHEME FOR THE TREATMENT OF CERTAIN NON-SPECIFIC FACTORS. I. Mirvish: South African M. J., 19:186-187, (June 9) 1945.

The author states that certain non-specific factors, such as emotional disturbances and fatigue, cannot only of themselves precipitate the asthmatic attacks, but failure to handle this aspect of the problem can completely wreck the most carefully devised scheme of medical treatment. The child as well as the disease must be treated. This demands a knowledge of the whole psychological background of the child—his relation to his parents, brothers and sisters, family, school teachers, and friends. The family practitioner, who occupies the role of "guide, philosopher and friend," is in the best position for studying the child in his environment, and the knowledge so gained when properly applied is of the utmost value in treatment.

The author gives an outline for a questionnaire with respect to the parents, the child, and school. He also gives some general instructions. The first of these is for the parents to be patient. There is no quick road to recovery, and ups and downs are to be expected. The parents are warned that the child is easily affected by the attitude of people about him. A cheerful, happy atmosphere tends to keep the condition in check, whereas an atmosphere of anxiety, nervousness, or tension is liable to precipitate an attack at any age.

As far as possible, the use of the term "asthma" or "attack" either in the presence of the child or others is to be avoided, and the child's ailments should not be discussed with other people, particularly in his presence, nor should he be compared with other children in his own presence.

The child should be encouraged to sleep alone. During an actual attack, excitement and panic are to be avoided. If the child is wheezing very mildly, do not draw his attention to it as this emphasis is almost certainly likely to make the attack worse. Fatigue must be guarded against. The commonest causes of chronic fatigue in a school child are: (a) insufficient rest; (b) irregular feeding habits; (c) too many "extras"—music lessons, dancing, et cetera.

The child must be treated, as far as possible, not as an invalid, but as a normal child.

CHEMICAL, PHYSICAL AND IMMUNOLOGICAL PROPERTIES OF ELECTROPHORETICALLY PURIFIED POLLEN EXTRACTS

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IN the past decade, notable achievements in the fields of physics and physical chemistry have given the biologist and the physician new tools to scrutinize more closely the relation of the constitution of matter to the causation of disease. In particular, the use of the electrical field and the gravitational field to analyze the movements of molecules has led to a deeper understanding of the size of proteins and of antigens in general. Among the new devices in particular are:

(a) Tiselius' moving boundary method of electrophoresis.
(b) The ultracentrifuge.
(c) Precision diffusion devices easily manipulated.

By means of these techniques, it has been made possible for my co-workers and myself to isolate, in the purest form apparently achieved thus far, the main colorless constituents found in pollen extracts of giant ragweed, dwarf ragweed and of timothy grass.[1-10] In addition, certain of the chemical and immunological properties of these major colorless molecules, as well as of the pigmented molecules, have been characterized. It has been found that the molecules responsible for clinical, pollen hay fever and asthma are not the large protein antigens which had hitherto been thought to be the specific immunological factors involved. Rather, my co-workers and I were surprised to find consistently that in these pollen extracts, as well as in all the other pollen extracts studied by us, the excitants of the symptoms of pollinosis were comparatively small molecules, having molecular weights not much more than 5,000, and having properties similar to but not characteristic of proteins. These molecules which have been isolated in highly purified form have been named as follows:

(a) In giant ragweed pollen *(ambrosia trifida)*, the main constituent has been called "Trifidin."

(b) In dwarf ragweed pollen *(ambrosia artemisiaefolia)*, the main constituent has been called "Artefolin."

(c) In timothy pollen *(phleum pratense)*, the main colorless constituent is now named, for the first time, "Pratensin."

METHODS

Figure 1 illustrates the moving-boundary method of Tiselius. The main portion, that is the side-arms and the connecting tubes, are merely electrode vessels. The actual electrophoretic separation of the

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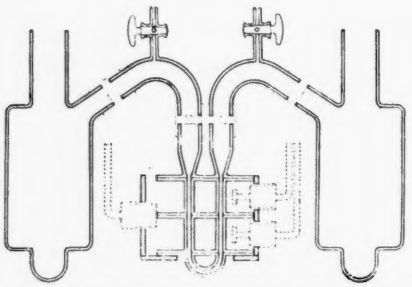
molecules occurs in the U-tube itself, which is in the central and lower part of the figure.

Figure 2 gives the dynamic process occurring in the electrophoresis cell with a three component mixture. Let us assume that three different



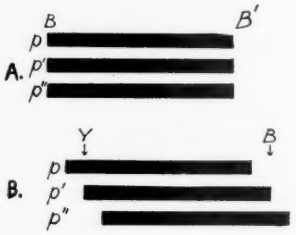


Fig. 1. *(left)* The moving-boundary method of Tiselius is illustrated in general. Note the large electrode arms and the small central U-tube with sliding sections. It is by means of these sliding sections that isolation of electrophoretically homogeneous fractions can be readily obtained.

Fig. 2. *(right)* This visualizes the dynamic process occurring in the electrophoretic cell with a three component mixture in the U-tube itself at the boundaries. When the uniform electric field is applied, proteins of different electrical mobility move at different speeds. By suitable sampling devices, the following fractions can be obtained: (a) Electrophoretically homogenous p. (b) Electrophoretically homogenous p''. (c) Mixed $p+p'$. (d) Mixed $p'+p''$. For further understanding of this process, see Figure 3.

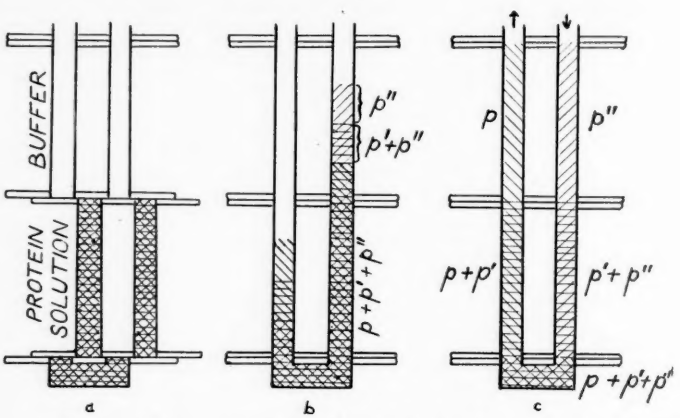


Fig. 3. The dynamics of electrophoretic fractionation is shown in the U-tube. Refer to Figure 2.

electrically charged proteins are present, with varying electric mobilities. If a uniform electric field is applied, the components will be moved to a new position as indicated in Figure 2(b). It is evident that by making a segregation at Y and at B, a portion of protein p and of protein p'' can be obtained in pure form. The same phenomenon occurs in the U-tube as illustrated in Figure 3. It was this technique, combined with special

optical methods of locating the boundaries which enabled us to isolate the main colorless constituents, Trifidin, Artefolin and Pratensin. In addition, it was this technique which also permitted the isolation of highly purified fast-moving pigments, especially in timothy pollen extracts.

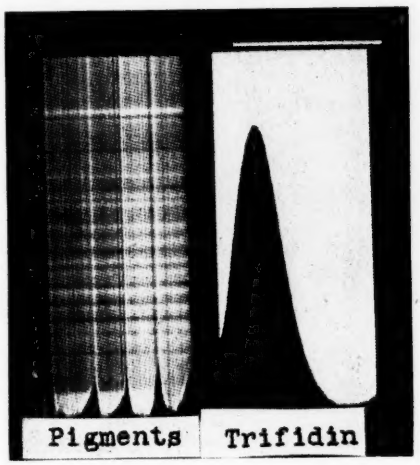


Fig. 4. The electrophoretic separation of the main colorless component Trifidin in giant ragweed pollen extract at ph. 6.5. The tall peak, labeled "Trifidin" is the main colorless component. The four smaller peaks on the left are produced by minor pigments. The actual electrophoretic migration occurs in a vertical position. The photograph has been rotated.

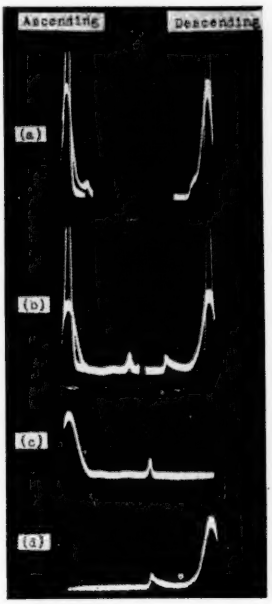


Fig. 5. The isolation of the fastest moving pigment in giant ragweed extract. This pigment is biologically active.

Indeed, it was possible to show that pigment fractions, free of the main components, Trifidin, Artefolin and Pratensin, gave skin reactions directly and by passive transfer.

ISOLATION AND IMMUNOLOGICAL PROPERTIES OF TRIFIDIN, ARTEFOLIN AND PRATENSIN

Figure 4 illustrates an experiment depicting the electrophoretic separation of the main colorless component, Trifidin, in giant ragweed extract. Illustrated also are four pigments. However, six or seven pigments have been observed and there is evidence that these are all biologically active.

Figure 5 illustrates the isolation of the fastest moving pigment in giant ragweed extract. This pigment is biologically active. In general, similar results were found for dwarf ragweed.

Figure 6 shows a successful electrophoretic analysis of timothy grass pollen extract with final isolation of Pratensin at the twenty-second hour.

As in the case of the ragweed extracts, there are numerous pigments labeled *p* in the figure. Similar results were found, but not without some differences, in the electrophoretic analysis of June grass, Bermuda grass, sheep sorrel, English plantain, birch and red oak. Indeed, our electro-

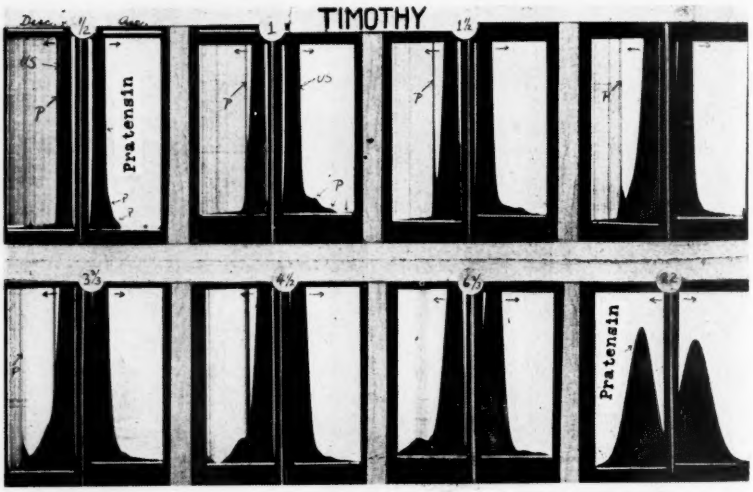


Fig. 6. The electrophoretic analysis of timothy grass pollen extract with final isolation of Pratensin at the twenty-second hour. Pratensin is the main colorless component. As in the case of ragweed extracts, numerous minor pigments are present. These are labeled P.

phoretic analysis showed a general similarity of all of the patterns with main colorless constituents and minor pigmented fractions, the activity of which, based on the evidence obtained thus far, indicates biological activity in both the pigmented molecules and the pigment-free colorless components.

ULTRACENTRIFUGAL AND DIFFUSION STUDIES ON TRIFIDIN AND ARTEFOLIN

As indicated in the foregoing, the electrophoretic technique enabled us to isolate the main colorless components of giant and dwarf ragweed pollen solutions. However, the size of the molecules was uncertain. We knew that these molecules were biologically active and, in addition, they diffused through ordinary collodion membranes. To obtain the approximate size of the molecules, the rate at which these molecules sedimented in the ultracentrifuge was ascertained. Figure 7 illustrates the actual sedimenting boundaries of Trifidin and Artefolin, compared with crude solutions of giant and dwarf ragweed themselves. Figure 8 shows the rates of sedimentation. Note that these molecules sediment out much more slowly than serum albumin. By correlating the ultracentrifugal data with diffusion studies, it was found that these molecules had molecular

weights of about 5,000 each. A molecular weight of 5,000 is rather low for the molecular weight of a typical protein. Indeed, considering the chemical reactions which will shortly be presented, it would appear that these molecules are closer to high-molecular-weight polypeptides, are more

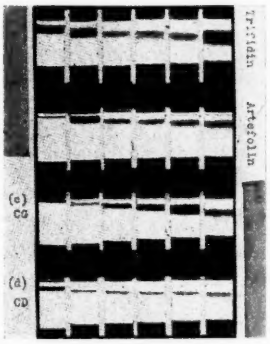


Fig. 7. The actual sedimenting boundaries of Trifidin and Artefolin in the ultracentrifuge are compared with crude pollen extracts of giant and dwart ragweeds. The rates of sedimentation are almost the same.

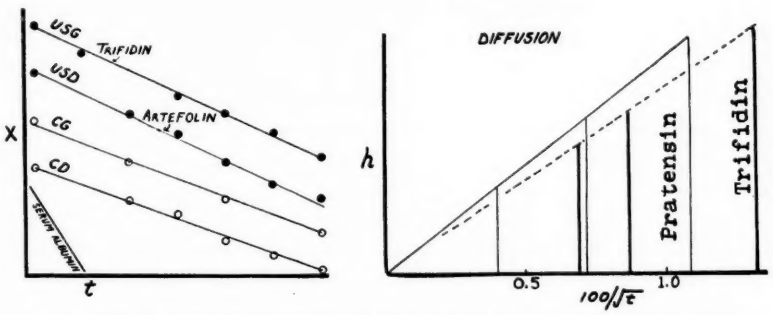


Fig. 8. *(left)* The rates of sedimentation of the boundaries in Figure 7 are plotted and compared with serum albumin. Note that serum albumin sediments in the gravitational field much more rapidly than Trifidin and Artefolin. This indicates that Trifidin and Artefolin have molecules which are comparatively smaller.

Fig. 9. *(right)* The diffusion rate of Pratensin is approximately the same as Trifidin, indicating that the molecular sizes are close to one another.

diffusible than proteins, can permeate the living system more readily, and show greater stability in the presence of heat.

Pratensin was also studied in the ultracentrifuge, but its molecule was not sedimented under the conditions of experiment. Diffusion studies, however, as illustrated in Figure 9, show that the molecule of timothy diffuses quite as rapidly as that of ragweed and, in all likelihood, has about the same molecular weight.

CHEMICAL ANALYSIS

The war interfered with more detailed studies of the chemistry and immunology of these highly purified fractions of pollen extracts. However, some experiments were performed. These results (Table I) compare the reactions of Trifidin and Artefolin with serum diluted 1:30. In

TABLE I. REACTIONS OF TRIFIDIN AND ARTEFOLIN ISOLATED BY ELECTROPHORESIS.

Test	*Trifidin*	*Artefolin*	*1:30 Serum*
Standing in ice box	Usually clear	Precipitate may form	
Phosphotungstic acid	Heavy precipitate	Heavy precipitate	Light precipitate
Millon	Positive	Positive	Positive
Biuret	Positive	Positive	Positive
Xanthoproteic	Deep yellow	Positive	Deep yellow
Trichloroacetic acid	Slight turbidity	Turbidity	Precipitate
Sulfosalicylic acid	Turbidity	Turbidity	Precipitate
Heller test	Slight opalescence	Slight opalescence	Positive
Heat and acetic acid	Opalescence	Opalescence	Opalescence
Molisch	Positive	Positive	

Note the lack of precipitation by trichlor acetic and sulfosalycilic acids.

our opinion, these reactions indicate that Trifidin and Artefolin are high-molecular-weight polypeptides, coupled with other molecules more or less formed like carbohydrate molecules, and that much more careful chemical work will be required on these fractions to determine their precise chemical nature. It is this type of experimentation, however, that will lead to the explicit evaluation of a chemical structure of a pollen antigen molecule.

DISCUSSION

Relationship of Molecular Size To Ease of Sensitization.

The general similarity of all of the electrophoretic patterns and the diffusion curves studied thus far indicates that we have to do with a new class of allergenic molecules, characterized by a molecular weight intermediate between those of typical proteins and polypeptides. Since the allergenic molecules are small, it is easy to understand how they can permeate the mucous membranes of the nose and other parts of the respiratory tract, to set up local and general allergic sensitivity. It is of interest to speculate that if the molecular weights of these allergenic molecules were 5,000,000 instead of 5,000, the frequency with which sensitization would occur should be much less because of the increased difficulty with which they would permeate the mucous membranes of the respiratory tract.

Rockwell,[12] using an independent method, has confirmed the molecular size reported here of these molecules. Further, Newell,[11] as well as Stone, Harkavy and Brooks,[13] among others, have all made important contributions to the chemical nature of allergenic molecules.

These and older investigations, having nearly all been recently surveyed in the excellent review of Wodehouse and Coca,[14] are not reviewed here.

Relation of Multiplicity of Components in Crude Extracts to Standardizations.

The experimental evidence unequivocally shows that pollen extracts are not simple antigenic solutions. They are complex mixtures, containing many components, the most different of which electrically, in the case of ragweed and timothy, are biologically active. The question arises: how justified is the position of those who insist that a chemical standardization procedure by phosphotungstic acid properly assays the biological activity of the extract? The implication contained in this point of view, that the phosphotungstic acid precipitable nitrogens of the various components are not only active but also equally active biologically, bears further scrutiny. I believe that the basic measure of allergic activity of a pollen extract must be a biological response; and only an immunological response like the eye, nose or skin reaction measures in a sensitized case the activity of an extract. A chemical determination at best is a secondary reference and, with our present knowledge, cannot be considered a standardization procedure. At best, it is a method of convenience. Which of these chemical methods of convenience is preferable, is open to question.

Future Investigations.

The technique described provides the investigator with electrophoretically homogeneous fractions, both colorless and pigmented. By our technique, only the colorless fractions have been successfully centrifuged in the experiments thus far performed. Whether or not pigmented molecules have smaller molecular weights than the colorless molecules cannot be stated. The retardation experienced in the gravitational field could be due to the shape and electrification of the molecule as well as to a smaller size. Rockwell, however, believes that certain of the pigmented molecules studied by him have molecular weights of about 1/5 of the colorless components. As mentioned, the war interfered with our studies planned to investigate the detailed immunological properties of the electrophoretically purified fractions. Experiments with Dr. G. Shwartzman on animal sensitization had been started before the war. Similarly, there remain for further study:

(a) The chemical characterization of the purified fractions.

(b) The role in which the various purified fractions produce sensitization and protection, studied especially by means of the new techniques to assay the differences between the sensitizing and the inhibiting antibodies.

(c) The interrelationships, both chemical and immunological, of the pigmented and the colorless forms.

It is only by the study of the characteristics peculiar to each component in the crude extract that basic immunological relationships can be established.

SUMMARY

1. The moving-boundary method of electrophoresis, the ultracentrifuge and diffusion techniques have been used to isolate and characterize the most highly purified fractions of pollen extracts thus far obtained.

2. It has been found that the molecules responsible for clinical, pollen hay fever and asthma are not large protein antigens but rather comparatively low-molecular-weight molecules, of the order of 5,000 or less, with chemical properties similar to but not characteristic of proteins.

3. Preliminary immunological and clinical studies indicate that pollen extracts are complex mixtures of many components with, however, a main colorless component readily isolated by means of the electrophoretic technique.

4. The main colorless component of giant ragweed extract has been named Trifidin, that of dwarf ragweed extract, Artefolin, and that of timothy extract, Pratensin. The relationship of the experiments described to the ease of sensitization, the standardization of crude extracts, and future experimental work, is briefly outlined.

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REPORT ON THE STANDARDIZATION OF DUST EXTRACTS

ADVISORY COUNCIL OF THE STANDARDIZATION COMMITTEE
GEORGE E. ROCKWELL, M.D., Chairman
J. WARRICK THOMAS, M.D.
FRED W. WITTICH, M.D.

THE Standardization Committee of the American College of Allergists was organized for the purpose of studying various methods of standardizing allergenic extracts.

More than a year ago this committee began a co-operative research program on the preparation and standardization of house dust extracts. This was the first extensive co-operative research ever undertaken in allergy. The program called for the preparation, chemical analysis, and skin testing of a series of extracts; and it was hoped that the data accumulated would indicate a practical and satisfactory method of standardization. Reports of the progress of the committee have appeared from time to time as editorials in the ANNALS OF ALLERGY,[6,7] and now sufficient data has been collected to permit a complete review of this work.

Samples of house dust were supplied by members of the Board of Regents of the College, and we wish to thank Drs. Hal M. Davison, French K. Hansel, Merle W. Moore, Harry L. Rogers, J. Warrick Thomas, Leon Unger, Orval R. Withers, and Fred W. Wittich for their co-operation in furnishing this material.

All of these dust samples were sent to Dr. Rockwell, and the extracts were prepared, chemically analyzed, sterilized, cultured for sterility, bottled, and distributed from his laboratory at Milford, Ohio.

To provide complete information on these extracts, we felt that they should be tested for skin reactivity on patients in various sections of the country; therefore, members of the College practicing in all parts of the United States, as well as some from Canada, Cuba, and Mexico, assisted in the clinical testing.

From the eight different samples of house dust we made twenty-four different extracts, thirteen of which were distributed to be tested for skin reactivity. A total of 365 patients were tested, and 3,224 individual skin tests were made. The following thirty doctors participated in the clinical testing: Drs. Wyndham B. Blanton, Ethan Allan Brown, Gerald M. Cline, Hal M. Davison, G. Estrada de la Riva, Stephan Epstein, Royal H. Finney, H. Harold Gelfand, Jerome Glaser, George A. Gray, O. C. Hansen-Pruss, Robert F. Hughes, M. Salazar Mallen, James A. Mansmann, John and William Mitchell, Merle W. Moore, Homer E. Prince, George E. Rockwell, Harry L. Rogers, Jacob W. Schoolnic, Willard S. Small, Robert Stier, J. Warrick Thomas, Leon Unger, Erich Urbach, Ira Wickner, Orval R. Withers, Fred W. Wittich, and Pearl Zink. We gratefully acknowledge their assistance.

PREPARATION OF THE EXTRACTS

Crude Extract. Two hundred or more grams of house dust were placed in a large flask and extracting fluid added to it. This solution contained 9 grams NaCl, 20 c.c. normal NaOH, and 1 c.c. of 10 per cent merthiolate per liter. Since the house dust samples varied a great deal, some were easily wet by the solution while others required twice as much liquid; enough was always used to completely wet the dust. It was allowed to extract at a cool temperature for forty-eight hours; then filtered through a Buchner funnel.

Crude Concentrate. The crude dust extract was concentrated by evaporation under vacuum or by placing it in cellophane tubing and passing dry air over it. After it was concentrated it was briefly and rapidly dialyzed against distilled water to remove the excess salt.

Alpha Picoline Concentrate. Alpha picoline was added to the concentrated crude extract until maximum precipitation occurred. This precipitate was collected, and then reprecipitated one or more times with alpha picoline or further purified by means of ammonium sulfate. In many respects the alpha picoline acts as acetone does, but is superior to it in most ways except for the disagreeable odor.

Absorbed Concentrate. The crude extract was concentrated and then made distinctly acid with HCl after which it was treated with an absorbing agent such as Lloyd's reagent or certain of the filter aides. The absorbing agent was then filtered off, washed with acid solution, and added to an extracting fluid which had a slightly alkaline pH. This educed the absorbed material from the absorbing agent. Such a preparation can be further purified by reabsorbing or by means of ammonium sulfate. The pH of the final preparation can be adjusted to neutrality and concentrated to the desired strength.

General Procedure. All of the dust extracts were Seitz filtered and cultured for sterility. At least six cultures were made from each extract using deep tubes and bottles of dextrose infusion broth. All extracts were diluted with 50 per cent glycerine by volume, then bottled under sterile conditions, and labeled.

IDENTIFICATION OF EXTRACTS

As each extract was prepared, it was assigned a symbol which was used for identification of the extracts sent out for testing. In this way there was no possibility of favoring one extract over another in reporting results and each extract could be judged fairly on its own merits. Samples of Endo's House Dust Extract were also bottled, given symbols, and sent out for testing along with the newly prepared extracts. The following key is furnished for identification of the extracts.

KEY FOR IDENTIFICATION OF DUST EXTRACTS

Source of Dust Sample	*Symbol for Dust Extract*	*Indentification*
Dr. Davison, Georgia	DA	Crude concentrate
	DB	A-picoline concentrate
Dr. Hansel, Missouri	HB	Crude concentrate
Dr. Moore, Oregon	MA	Crude concentrate
	MB	A-picoline concentrate
Dr. Rogers, Pennsylvania	RB	Crude concentrate
Dr. Thomas, Virginia	TB	A-picoline concentrate
	TD	Crude concentrate
Dr. Unger, Illinois	UF	Crude concentrate
Dr. Withers, Missouri	WX	Absorbed concentrate
	WY	Crude concentrate
Mixed Dust	AA	Absorbed concentrate
	AB	Crude concentrate
Endo's House Dust Extract	DC	
	MC	
	RA	
	TA	

CHEMICAL ANALYSIS OF EXTRACTS

All solutions were brought to 20° C. for volumetric measurement. All determinations were made in duplicate.

Determination of Total Nitrogen. The total nitrogen determinations on these extracts were made by the micro Kjeldahl method, using a small sample, preferably .5 to 1 c.c. This determination was made before the glycerine was added.

Determination of Phosphotungstic Acid Precipitate Nitrogen. This determination can be made before or after glycerine is added.

Ten c.c. of extract were precipitated with 5 c.c. of concentrated HCl and 5 c.c. of phosphotungstic acid reagent (10 per cent phosphotungstic acid in 10 per cent HCl). It was mixed thoroughly in a centrifuge tube and allowed to stand for 24 hours at near freezing temperature. The precipitate was separated by centrifugal force, and the supernatant fluid was tested with more concentrated HCl and phosphotungstic acid reagent to be sure that all of the phosphotungstic acid nitrogen had been precipitated.

The precipitate was then washed with 2 c.c. of a cold solution of ammonia-free water containing the same proportion of HCl and phosphotungstic acid reagent as were used for precipitation. It was chilled again, separated, and the supernatant fluid decanted. This was repeated once. Then the sides of the tube and surface of the precipitate were rinsed with 2 c.c. of cold ammonia-free water.

Two c.c. of ammonia-free water and one drop of phenolphthalein indicator were added to the precipitate. Enough NaOH was added to completely dissolve the precipitate, and after it was entirely in solution, a drop of acetic acid was added, or enough to make it definitely acid; then

it was washed into a 25 c.c. volumetric flask and diluted to volume with ammonia-free water.

Total phosphotungstic acid precipitate nitrogen was determined by the micro Kjeldahl method, using a 2 c.c. sample.

Free alpha amino nitrogen of the phosphotungstic acid precipitate was determined by the Van Slyke manometric method, using a 5 c.c. sample. Before determining the unknown sample the accuracy of the apparatus should be checked by running a known solution of glycine (1 mg. per c.c.).

Determination of Molecular Size. The phosphotungstic acid precipitate has erroneously been referred to as the protein nitrogen. Unfortunately this precipitate brings down not only proteins but peptides of all sizes and certain basic amino acids. Hence, it does not represent protein nitrogen but rather a mixture of any proteins (if present), peptides of all sizes, and certain amino acids (if present). But in dust extracts it is the best method available for separating peptides and any proteins from the other nitrogenous material present. Therefore, we shall consider the phosphotungstic acid nitrogen as the total nitrogen of the antigens present in dust extract.

Peptides, polypeptides, and proteins each have one free alpha amino nitrogen per molecule. Therefore, by dividing the total nitrogen of the phosphotungstic acid precipitate by the free alpha amino nitrogen we find the number of nitrogen atoms present in each molecule of the peptide or protein. This indirectly gives information on the size of the molecule present. Such calculations will be in error in proportion to the amount of nonspecific substances present in the phosphotungstic acid precipitate, and any specific antigen present which may not have been precipitated by the phosphotungstic acid.

TESTING AND EVALUATION OF EXTRACTS

Method of Testing Extracts. In order that the testing of these extracts be uniform, a set of directions for skin testing was prepared by the Advisory Council of the Committee. The directions set forth were as follows:

1. All tests are to be made intradermally.
2. Please keep antigens in refrigerator when not being used.
3. Use properly cleaned and sterilized sharp 26-gauge hypodermic needles and tuberculin syringe.
4. The amount injected should be constant and accurately measured for all tests, and recorded on the data sheet.
5. The dilutions to be used will be indicated in the letter sent out with the extracts.
6. Injections: Make injections approximately 2 inches apart with the least possible trauma in the volar surface of the forearm and lateral surface of the arm. Injections are preferably made by the same individual so that the technique will be about the same.
7. Reactions: Skin reactions may be read with a 75-watt Mazda lamp or by daylight. Observations of the skin reactions should be made at fifteen minutes and readings taken about twenty minutes after the injections. When the wheals and

flares are of their maximum size they should be recorded by one of two methods: (a) Tracings: The wheals and flares are outlined on the skin with a washable ink. Thin tissue paper is placed over them and both the wheal formation area and erythema are traced in pencil. These tracings should then be transferred by means of carbon paper to the enclosed data sheet. (b) Measurements: The wheal and flare should be measured in centimeters and recorded as wheal/flare; for example, a wheal measuring 1 x 1 cm. with a flare of 2 x 4 cm. should be recorded as 1x1/2x4. A notation of "ps" should be made if pseudopodia develop; thus, if there were pseudopodia, it would be recorded as 1x1/2x4 ps.

Each doctor was asked to make four dilutions of the extract: namely, 1:10, 1:100, 1:1000 and 1:10,000. The house dust-sensitive cases were to be tested with all four dilutions and the controls with the 1:10 and 1:100 dilutions. The results were recorded on special sheets furnished for the purpose.

Method of Evaluating Skin Reactions. The following system was devised for the evaluation of skin reactions:

1. Only the wheal was considered.
2. The wheal was carefully measured in millimeters and the average diameter computed.
3. If the amount of extract injected was .01, .02, or .03 c.c., no consideration was given to it; however, if .05 c.c. was injected, the average diameter of the wheal was divided by 2.
4. The highest dilution was considered first; if the wheal measured less than 5 mm. in average diameter, it was disregarded and the next lowest dilution was judged and so on.
5. Scale of values:

Dilution	*Average Diameter of Wheal in Millimeters*	*Rating of Skin Reactivity*
	10 or more	6
1:10,000	8 or 9	5
	5, 6, or 7	4
1:1,000	5 or more	3
1:100	5 or more	2
	3 or 4	1

RESULTS

We felt that the simplest way to present the results of such an extensive experiment would be to assemble the data in charts and tables, each designed to illustrate or prove a point in question. This we have endeavored to do.

Comparison of Total Nitrogen and Skin Reactivity. Table I shows the total nitrogen and skin reactivity of five different dust extracts. Note that the total nitrogen varies greatly and compare this variation to the skin reactivity.

From these results it is obvious that total nitrogen content and skin

reactivity of an extract have no direct relation to each other. This lack of correlation is emphasized by the fact that several of our extracts with widely different total nitrogen content gave almost identical skin reactions.

TABLE I. NO DIRECT RELATION BETWEEN TOTAL NITROGEN CONTENT AND SKIN REACTIVITY OF A DUST EXTRACT

Dust Extract	Total Nitrogen mg. per c.c.	Rating of Skin Reactivity
AA	0.3594	4.12
WX	0.3722	5.00
RB	0.8200	4.11
UF	1.6010	3.90
WY	2.1277	4.85

TABLE II. DUST EXTRACTS WITH WIDELY DIFFERENT TOTAL NITROGEN CONTENT GAVE ALMOST IDENTICAL SKIN REACTIONS IN PATIENTS*

Extract	Patient: S. S.	Patient: T. A.
AA 1:100 Dilution Total Nitrogen 0.3594 mg. c.c.		
WX 1:100 Dilution Total Nitrogen 0.3722 mg. c.c.		
WY 1:100 Dilution Total Nitrogen 2.1277 mg. c.c.		

* Tests done by Dr. Salazar Mallen.

This is shown in Tables II and III with tracings of individual skin reactions.

From Tables II and III one notes that in the four extracts the total nitrogen varies from 0.3722 to 2.1277 mg. per c.c., yet the skin reactions are identical within experimental error.

TABLE III. DUST EXTRACTS WITH WIDELY DIFFERENT TOTAL NITROGEN CONTENT GAVE VERY SIMILAR SKIN REACTIONS IN PATIENTS*

Extract	Patient: Mrs. L. F. Dilutions of Extract 1:100	1:1,000	1:10,000	Patient: Miss M. M. Dilutions of Extract 1:100	1:1,000	1:10,000
WX Total Nitrogen 0.3722 mg. c.c.						
RB Total Nitrogen 0.8200 mg. c.c.						
WY Total Nitrogen 2.1277 mg. c.c.						

* Tests done by Dr. S. Epstein.

Comparison of Skin Reactivity and Phosphotungstic Acid Precipitate Nitrogen. Cooke[4,5] has contended that the phosphotungstic acid precipitate nitrogen of pollen extracts contains the active antigen. Although this has been questioned by others[1,2,3] and may not be absolutely true, it still remains the most practical and convenient method of separating the active antigens from the crude dust extracts. If the antigens of all dust extracts are exactly alike, then standardization by the total nitrogen of the phosphotungstic acid precipitate should be accurate; and this total nitrogen should have a definite sequence with the amount of skin reactivity of such antigens.

Table IV lists eleven extracts with increasing amounts of phosphotungstic acid precipitate nitrogen; however, there is no uniformity or regular sequence in the molecular size of the antigens. In this group the number of nitrogen atoms varies from 4 to 14 per molecule.

From this table it is evident that the skin reactivity rating does not absolutely follow the variations in the phosphotungstic acid precipitate nitrogen although it does so more than it follows the total nitrogen content.

Molecular Size. In contrast to the preceding experiment, six extracts were selected whose antigens were approximately the same molecular size, varying only from 9 to 14 nitrogen atoms per molecule. These extracts were diluted so that the phosphotungstic acid precipitate nitrogen was con-

stant at .300 mg. per c.c. From these we made dilutions of 1:100 and 1:1,000 which were sent out for skin testing. Each patient was tested with all six of the extracts in both dilutions, thus the results make it possible to

TABLE IV. SKIN REACTIVITY OF DUST EXTRACTS IN RELATION TO THEIR PHOSPHOTUNGSTIC ACID PRECIPITATE NITROGEN CONTENT, BUT NOT IN RELATION TO THEIR MOLECULAR SIZE.

Extract	Phosphotungstic Acid Precipitate Nitrogen mg. per c.c.	Rating of Skin Reactivity
TD	0.1360	3.60
DB	0.1407	3.76
AA	0.3064	4.12
WX	0.3238	5.00
AB	0.3710	4.37
TB	0.5346	4.00
MA	0.5515	4.05
RB	0.7065	4.11
MB	0.8530	4.47
UF	0.9680	3.90
WY	1.2843	4.85

TABLE V. SKIN REACTIVITY OF DUST EXTRACTS WHICH CONTAIN EXACTLY THE SAME AMOUNT OF PHOSPHOTUNGSTIC ACID PRECIPITATE NITROGEN AND IN WHICH THE ANTIGENS ARE APPROXIMATELY THE SAME MOLECULAR SIZE.

Extract	Phosphotungstic Acid Precipitate Nitrogen mg. per c.c.	Rating of Skin Reactivity
AA	0.300	3.57
RB	0.300	3.71
UF	0.300	3.57
WX	0.300	3.52
MB	0.300	3.47
MC	0.300	3.52

compare these extracts one with another. Table V shows these results.

From Table V it is apparent that when dust extracts are selected so that the molecular size of the active antigen is approximately the same, the skin reactivity is dependent upon the phosphotungstic acid precipitate ni-

trogen. In other words, dust extracts standardized on a molar basis can be made identical so that their skin tests are identical. To further illustrate this, Table VI shows tracings on three different patients with this series of extracts.

TABLE VI. TRACINGS OF SKIN REACTIONS WITH DUST EXTRACTS WHICH CONTAIN EXACTLY THE SAME AMOUNT OF PHOSPHOTUNGSTIC ACID PRECIPITATE NITROGEN, AND IN WHICH THE ANTIGENS ARE APPROXIMATELY THE SAME MOLECULAR SIZE*

Extract	Patient: L. B.		Patient: R. D.		Patient: M. Def.	
	Dilutions of Extract		Dilutions of Extract		Dilutions of Extract	
	1:100	1:1,000	1:100	1:1,000	1:100	1:1,000
AA						
RB						
UF						
WX						
MB						
MC						

* Tests done by Drs. G. A. Gray and G. E. Rockwell.

Effect of Regional Distribution on Skin Reactivity. The samples of dust used in this work were collected in various parts of the country, and the extracts made from them were skin tested in numerous places, which afforded an opportunity to study the effect of regional distribution. Table VII lists the source of the extract and the testing regions together with the rating of skin reactivity in each region. All of the extracts were sent to doctors in various regions, however, some did not respond, hence this summary is not complete.

TABLE VII. SIX SOURCES OF DUST SAMPLES LISTED IN THE VARIOUS STATES IN WHICH THEY WERE TESTED, TOGETHER WITH THEIR RATING OF SKIN REACTIVITY IN THAT STATE.

Georgia	Virginia	Missouri	Illinois	Oregon	Pennsylvania
Canada 3.6	Va. 3.6	Ohio 2.6	N.Y. 3.7	Oregon 4.6	Penna. 4.2
Penna. 3.4	Mass. 3.4	Oregon 2.2	Ohio 4.2	Ill. 3.0	Ohio 2.6
Wash. 3.9	Ohio 4.8	Cuba 3.0	Penna. 3.8	Texas 4.2	Oregon 3.7
	Mo. 4.6		Texas 3.6	N.C. 3.0	Wisc. 5.0
	Texas 3.5			Minn. 5.3	
	Calif. 4.0				

TABLE VIII. INDIVIDUAL VARIATIONS IN SKIN REACTIONS*

Extract	Case 1 Dilutions of Extract			Case 2 Dilutions of Extract		
	1:100	1:1,000	1:10,000	1:100	1:1,000	1:10,000
RA						
RB						
TB						
TD						
DA						
DB						

* Tests done by Drs. W. F. Mitchell, O. R. Withers, and R. F. Hughes.

Table VII shows that although there is some variation from region to region it is not as great as one might expect. Undoubtedly an active dust extract will give a positive skin test in any section of the country.

Individual Variations in Skin Reactions. Although there is not much variation in skin reactivity in one region as compared to another, we have

repeatedly noticed in this collective study that there are many individual variations in skin reactions. We have selected a few reports to illustrate this point in Table VIII.

TABLE IX. SKIN REACTIVITY OF ALPHA PICOLINE CONCENTRATES COMPARED TO CRUDE CONCENTRATES.

Extract	Phosphotungstic Acid Precipitate Nitrogen mg. per c.c.	Rating of Skin Reactivity	Rating of Skin Reactivity of the Corresponding Crude Concentrate
DB	0.1407	3.76	3.69
TB	0.5346	4.00	3.60
MB	0.8530	4.47	4.05

TABLE X. TRACINGS OF SKIN REACTIONS WITH THREE DIFFERENT ALPHA PICOLINE CONCENTRATES*

Extract	Dilutions of Extract		
	1:100	1:1,000	1:10,000
TB			
DB			
MB			

* Tests done by Drs. R. F. Hughes, O. R. Withers, and F. W. Wittich.

You will note from this table that in one case one extract appears to be stronger and in another case the results are reversed, thus emphasizing individual variation.

Dust Extracts Purified and Concentrated by the Alpha Picoline Method. These extracts are potent and are an improvement over the crude concentrates. This is shown in Table IX, in which we have tabulated a few of

them together with the concentrated crude extract made from the same dust sample.

From Table IX it is noted that the alpha picoline extract has more skin

TABLE XI. AMOUNT OF PHOSPHOTUNGSTIC ACID PRECIPITATE NITROGEN AND THE SKIN REACTIVITY OF TWO ABSORBED CONCENTRATES AND ENDO'S DUST EXTRACT.

Extract	Phosphotungstic Acid Precipitate Nitrogen mg. per c.c.	Rating of Skin Reactivity
AA	0.3064	4.12
WX	0.3238	5.00
Endo	0.4090	4.25

TABLE XII. TRACINGS OF SKIN REACTIONS WITH TWO DIFFERENT ABSORBED CONCENTRATES*

Extract	Dilutions of Extract		
	1:100	1:1,000	1:10,000
AA			
WX			

* Tests done by Drs. W. B. Blanton and S. Epstein.

reactivity than does its corresponding crude concentrate. This is further illustrated in Table X, which shows individual tracings of typical skin reactions due to alpha picoline extracts.

Extracts Purified and Concentrated by the Absorption Method. The skin reactivity ratings of these extracts together with their phosphotungstic acid precipitate nitrogen contents are shown in Table XI along with Endo's for comparison.

From Table XI it is noted that although the phosphotungstic acid precipitate nitrogen in the preparations purified and concentrated by the absorption method is much lower than that of Endo's extract, the skin reactivity is approximately as high in one instance and higher in another

than is Endo's. Thus it is evident that these extracts are potent and biologically active.

To further illustrate this, Table XII shows actual tracings of tests done with extracts purified and concentrated by the absorption method.

From Table XII it is evident that these extracts purified and concentrated by absorption are capable of giving good wheal reactions in sensitive cases.

CONTROLS

In any skin test the matter of control must be considered. Controls for a series of tests such as we are reporting might be divided into two groups: (a) nonallergic controls and (b) allergic but clinically nondust-sensitive controls.

We felt that if the concentrated dust extract was to mean anything it should give a positive test in at least a 1:100 dilution in a dust-sensitive patient; and correspondingly should give a negative test in 1:100 dilution in a control. Therefore, our controls were tested in a dilution of 1:100. However, this may lead to confusion because one extract may be much more concentrated than another and a 1:100 dilution of it would be a stronger extract than a 1:100 dilution of the other. The responses on our questionnaire were not sufficient for us to divide our cases into nonallergic controls and allergic patients who were nondust-sensitive, therefore, we shall have to consider them as a whole.

Our crude concentrated extracts tested 40.5 per cent negative and 59.5 per cent positive (rating of 1 and occasionally of 2) in the controls. The picoline concentrates gave 45.5 per cent negative reactions and 54.5 per cent positive; whereas our absorbed concentrates gave 57.9 per cent negative and 42.1 per cent positive reactions. In comparison, Endo's dust extract sent out under code symbol gave 51.7 per cent negative and 48.3 per cent positive reactions in the controls.

As mentioned above, however, one cannot accept these figures exactly on their face value. If we arbitrarily conclude that a 1:100 dilution should contain .003 mg. phosphotungstic acid precipitate nitrogen per c.c., then on such basis our crude extract was a dilution of 1:67 and not 1:100. Our absorbed concentrate still remains 1:100, whereas the picoline concentrate would be a dilution of 1:59 and Endo's would be a dilution of 1:73. Recalculated on this basis our results would be: Crude concentrate gave 40.5 per cent negative skin reactions in a dilution of 1:67; picoline concentrate gave 45.5 per cent negative in a dilution of 1:59; absorbed concentrate gave 57.9 per cent negative in a dilution of 1:100; and Endo's extract gave 51.7 per cent negative in a dilution of 1:73.

What these extracts would have shown in the controls had they all been diluted to contain .003 mg. phosphotungstic acid precipitate nitrogen per c.c. (our theoretical 1:100 dilution) is hard to estimate. Again, what constitutes a negative reaction needs to be more clearly defined, and this

will undoubtedly require further studies. From our work on this experiment we would conclude that the smallest positive reaction should be a wheal of at least 5 mm. diameter in a dilution of 1:100. However, it is evident that our crude concentrated extracts gave a higher percentage of positives in controls than did Endo's; our absorbed concentrates definitely gave fewer positive reactions in the controls than did Endo's; and our picoline concentrates gave approximately the same number of positives as did Endo's.

STANDARDIZATION

We feel that any standardization of dust extract must be done both biologically and chemically. Specifically we recommend that standardization of dust extract give the following information: (1) the total nitrogen, (2) the phosphotungstic acid precipitate nitrogen, and (3) the relative number of nitrogen atoms per molecule of antigen. And we recommend that the dust extract should meet the following specification: when it is diluted to contain .003 mg. phosphotungstic acid precipate nitrogen per cubic centimeter it should give a positive reaction in known dust-sensitive cases and a negative reaction in known controls.

This data furnishes the following information: (1) the amount of nonspecific nitrogen present, namely, the difference between the total nitrogen and the phosphotungstic acid precipitate nitrogen; and (2) the relative number of molecules of active antigen present and also the relative size of these molecules. The skin tests will tell whether or not the antigen is biologically active, and the controls will show whether or not there is any nonspecific reaction present.

Some people feel that standardization of dust extracts is not necessary and possibly even undesirable. We question very much if it is possible to make two dust extracts exactly alike unless they are standardized by both chemical and biological methods. We doubt very much if there is any dust extract on the market which, lot after lot, bottle after bottle, will be exactly the same. For instance, in our experiments we sent out Endo's extract under code number to the various testing members. All of the samples sent out were from one lot so that all results would be uniform. However, some of the members, not knowing that Endo's was among the extracts they were testing, tested with their Endo's and sent back reports that were different from the Endo's which they unknowingly tested in code number. This prompted us to obtain another lot and analyze it chemically. The lot that we sent out contained .409 mg. phosphotungstic acid precipitate nitrogen per c.c. whereas the second lot contained only .310 mg. per c.c.

SUMMARY AND CONCLUSIONS

Methods are given for preparing the extracts known as crude concentrate, alpha picoline concentrate, and absorbed concentrate; also the various methods of analysis are given.

Data is presented which definitely shows that there is no relation between skin reactivity and the total nitrogen present in an extract. Evidence is presented which shows that although there is some relation between skin reactivity and the phosphotungstic acid precipitate, nitrogen, it at best is not too good when there is appreciable variation in the molecular size of the dust antigen. However, when extracts were selected whose antigens were of approximately the same molecular size, and when they were adjusted so that the phosphotungstic acid precipitate nitrogen was constant, their skin reactivities were alike within the limit of the experimental error of such tests. Evidence is presented showing the skin reactivity of dust collected in various parts of the country and then subsequently tested in various regions. The variance indicates that there is not as much discrepancy in skin reactivity between the various sections of the country as there is in individual variations.

It is concluded that extracts, purified and concentrated with alpha picoline or by the absorbed method, are potent extracts, with characteristics which improve them over crude extracts or any other extracts to which they have been compared.

It is concluded that successful standardization of dust extract can be done by a combination of chemical and biological methods. The standardization chemically involves the determination of total nitrogen; and the total and free alpha amino nitrogen of the phosphotungstic acid precipitate. It is pointed out that such extracts should then be tested biologically and dilutions be made based upon their chemical analysis—namely, dilutions so that the extract contains .003 mg. of phosphotungstic acid precipitate nitrogen per cubic centimeter. Such an extract should be capable of giving a positive reaction in a known dust-sensitive case and a negative reaction in a normal individual.

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CLINICAL AND COMPARATIVE ALLERGY

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MODERN medicine is built on a fundament of experimentation. Experimentation is observation under controlled conditions. And man is both the most desirable and for obvious reasons the least available subject of experimentation. For this reason, one of the most important steps in the development of modern medicine was the recognition of the concept of the essential similarity of the organization of all living matter. This would sound trite were it not for the fact that allergy is usually treated as if it were an affliction particular to the human race. Zinsser[16] formulated this notion very prettily when he said that man "possesses an immaculately conceived type of sensitivity, that, like his soul, distinguishes him from the animal kingdom." This certainly is a prejudice. We have a number of reports on allergic diseases in animals —particularly horses, cattle and dogs.[14] Some reports may not be as well substantiated as is expected in human medicine. Others are. A good example is F. W. Wittich's study and presentation of a dog with hay fever.[15] L. Reddin, Jr.,[11] and R. Povar[9] presented interesting clinical observations today. Allergists have reason to be grateful for those papers because they concern a point vital for the speedy development of allergy. For good measure, I am showing the head of a walrus baby, which was observed by C. R. Schroeder[12] for a skin infection resembling eczema. This walrus baby was bottle fed, and Dr. Schroeder at once had the correct conception of the nature of the disease. He suspected that it might be connected with the unnatural food, and he was able to prove this point. He put the little walrus on a fish diet, and the eczema promptly improved. This is a remarkable case, one of the earliest clear-cut observations in any animal and, as far as I am aware, still the only one in a wild animal. But beyond that, I wish that allergists would remember this head each time they wonder about the basic problems of allergy. I want it remembered as a symbol that our friends, the animals, are ready to help in the exploration of allergic phenomena just as much as in other problems of physiology and pathology, if we only are willing to ask them the right questions.

As a matter of fact, the history of supersensitivity starts with animals because anaphylaxis was first observed in goats and dogs. And it then turned out that the guinea pig had been created especially for the purpose of anaphylactic experimentation. Anaphylaxis, of course, is different in important but not basic aspects from other phenomena of supersensitivity. Experiments in anaphylaxis have been done on a number of species, as guinea pigs, rabbits, rats, mice, and dogs. But experi-

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mentation on other forms of supersensitivity have been done in the main on the guinea pig. Dermal sensitization to various antigens and haptens can be classically demonstrated and studied in the guinea pig, and the same is true with tuberculin sensitivity.[1,8] If one adds the work on the

Fig. 1. Head of the milk allergic walrus baby (courtesy of Dr. C. R. Schroeder).

sensitization of rhesus monkeys by Straus and Coca,[13] the work in cattle on sensitization to ragweed,[14] and the work on serum sickness in rabbits by Fleischer and his co-workers,[4] the list is almost exhausted. Thus, it is small wonder that allergy has not harvested the benefits other fields of medicine have derived from experimentation. However, as allergic edema, eczema and hay fever have been found in other animals, it should be possible to select the proper animal for experimentation of the various problems causing concern. Moreover, from what data there is, it appears likely that where local allergic sensitization is passively transferable, this transfer can be effected from one species to another. This should greatly facilitate the comparative evaluation of observations in different species. Altogether, a whole nearly unexplored field of research is open here for the mutual benefit of human and veterinary medicine, promising a harvest valuable in itself and able to create tools for experimentation.

To enlarge a little on some of the problems waiting for the proper experimental approach, those of heredity are of particular importance. Present knowledge of the hereditary factors in allergy is general, rather than detailed. In animals bred for utility, for example, one would expect that breeding tends to eliminate inherited allergic factors. On the other hand, it is remarkable how many of the reports on allergy in animals refer to inbred stock. Dr. Povar's experience[9] in this respect

is quite characteristic. Systematic exploration of the hereditary factors in animals would certainly be an object in fundamental interests. Landsteiner[8] was one of the first to realize that. In his laboratory Chase[1] was able to show that in guinea pigs, within a few generations, the propensity to become sensitized can be greatly enhanced. The use of stock selected from this point of view has greatly contributed to the success of the work of Landsteiner and Chase. It is of particular interest that guinea pigs selected by sensitization to dinitrochlorobenzene were also found to be more uniformly sensitized to poison ivy and, inversely, a stock of low susceptibility to dinitrochlorobenzene was inferior in ability to become sensitized to picrylchloride. It appears also that the Rockefeller stock is of high susceptibility to anaphylactic sensitization.[2] Though these data do not concern a highly inbred strain, and despite the circumstance that Chase noted several exceptions to the rule, the general trend of the experience is akin to that in man. Namely, what is inheritable in allergy is not so much the propensity of acquiring sensitization to a given antigen, but the general propensity to sensitization as such, or rather the propensity to acquire a certain class of sensitization. Coca's data[3] indicate that certain types of sensitization may have an independent mechanism of inheritance. No doubt it would be most fascinating if this could be confirmed and elaborated upon by experimentation.

Another problem awaiting analysis by experimentation is that of subclinical sensitization. When testing cows with ragweed extracts,[10,14] we found 40 per cent definitely skin-sensitive, but there was no indication of clinical affection. This is an observation of some clinical interest because positive skin tests without clinical manifestations are well known to every one of us, and we all know that they constitute a considerable source of incertitude and a frequent source of error. We are maybe a bit too much inclined to avoid this problem by just labeling such reactions as unspecific. I, personally, and I am sure a great many others, will have our doubts whether a competently made skin test—a test performed with all necessary controls and precautions—is actually ever unspecific. It is easy to hide behind this word, but it would be better to spend some thought on the problem involved. To me, a much more likely working hypothesis would be that sub-clinical sensitization is very frequent. The epidemiologist will state that an exactly parallel situation exists in the field of infectious diseases. The number of actually clinically sick persons in a population may represent only a small percentage of those infected. Information on the mechanism of epidemics has greatly gained by the recognition of this fact. I would suppose that further experimental evidence of the frequency of subclinical sensitization may be very helpful in our attitude to clinical problems.

There is, furthermore, the whole complex problem of the mechanism of sensitization beyond the primary factor of antibody response to an antigen. This fundamental problem can only be approached properly

if the spade work has been done which will give the proper experimental setup.

As the last point, the question of the quantitative relations in allergic reactions should be mentioned, if only to lament our ignorance. It is known that extremely small amounts of antigen are needed both for shock and particularly for sensitization, but very little is clear about the quantitative relations between antigen and antibody even in those cases where circulating antibody has been demonstrated. The best approximation of such quantitative data is found in Kabat's work[6,7] on passive sensitization of guinea pigs. From these papers it appears that antibody in the order of 0.5 mg. per kg. body weight will sensitize practically 100 per cent of the animals. This figure looks rather small. However, if one considers that the antibody, like a drug, must localize in the body's cells, it becomes apparent that this figure is well within the order of magnitude of effective doses for numerous pharmacologically active compounds as, for instance, atropine and digitalis. Moreover, the effective antibody dose is calculated for total body weight, and there is good reason to believe that antibody molecules are not fixed in the body at random, but are concentrated in certain cells.

The antigen-concentration necessary for shock was found by Kabat to be several milligrams per guinea pig and this was found to be true for a proteinic antigen (crystalline ovalbumin) and a carbohydrate (pneumococcal S-substance). This means a dose in the order of 10 mg. per kg. body weight is needed. The randomness of antigen distribution is not known. However, the fact that it is immediately effective for shock makes it likely that it is more evenly distributed than is the antibody, which has to be fixed by the cells, as testified by the period of lag which is in the order of many hours.

Kabat feels that his figures suggest that optimal conditions for anaphylaxis are found in the region of considerable excess of antigen. Because of the uncertainty concerning the randomness of distribution, I feel that this conclusion is not yet proven. If antibody is concentrated in relatively few cells—what has been called shock tissue—a fraction only of the antigens circulating in the blood may be available for reactions, and this would possibly shift the ratio of antigen nearer to the point of equivalence known from *in vitro* measurements. This view is also supported by an evaluation of the data which were obtained in neutralization tests in the skin of cattle.[14] In this case one can calculate that antibody in the order of micrograms neutralized 5 to 25 $\mu\gamma$ of the ragweed extract. If it is taken into account that the unpurified extract used certainly contains only a small percentage of active antigen, one immediately sees that in this case of a local effect there could be present no considerable excess of antigen.

In his papers, Kabat points out that the concentrations of immune antibody necessary for anaphylactic sensitization are well below those

needed for the formation of visible precipitates in the test tube. Accordingly, he proposed as a working hypothesis that the lack of visible *in vitro* reaction of serum from allergic diseases may be explained by a mere concentration factor. In other words, he suggests—as have others (Zinsser)—that quantitative considerations may offer an alternative to the usual conception that allergic antibodies are qualitatively different from immune antibodies. The difference between immune and allergic antibodies in heat stability, in local fixability in the tissue, and in ability to passively sensitize the guinea pig's smooth muscles, militate against such a viewpoint. It remains, however, worthwhile to look for direct evidence for or against the quantitative alternative. It appears quite possible that the refinement in the determination of antibodies worked out in recent years in Heidelberger's laboratory may be of great help for this purpose. This method[5] allows one to measure with considerable exactitude amounts of antibody in the order of micrograms.

The scientific program of the American College of Allergists emphasizes work on the purification of antigens. Progress in this field will be a most important complement to the experimental exploration of the quantitative relations.

I hope that this summary of the present knowledge of allergy in animals and its relation to medical allergy will demonstrate the desirability of building up this field of endeavor. Allergy is not an affliction peculiar to man, and a realization of this cannot but be helpful in making the whole complex field appear as the expression of a basic physiological mechanism. The few examples given here will encourage our faith that systematic experimentation in animals will become eventually as important a complement to clinical observations as it has proven to be in other fields of medicine.

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HAY-FEVER PLANTS OF ALBUQUERQUE, NEW MEXICO

A Preliminary Report

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E. L. STORMFELS, A.B.
Albuquerque, New Mexico

THIS is a report on the 1945 hay-fever season for Albuquerque, New Mexico. Its purpose is to outline the hay-fever problem for an area of mild and arid climate to which many sufferers come seeking relief from respiratory ailments.

Although the literature on hay-fever plants is replete with regional reports (Wodehouse,[5,6] Gottlieb and Urbach[2]), the problem varies from locality to locality. In the existing literature the states of New Mexico, Arizona and western Texas are treated regionally as the Southwest. Texas and Arizona have a reasonable presentation of local problems done by various authors. However, only one area thus far has been reported for New Mexico, Gallup by Watry and Lamson.[4]

The variety of the flora in New Mexico, especially in Albuquerque and the Rio Grande River valley, presents a serious and complicated hay-fever problem. The present report presents the species of pollen present, as nearly as possible, the exact beginning and ending of the pollination period of each, and their clinical significance in Albuquerque.

Albuquerque stands at an altitude of 5,000 feet in the Rio Grande valley. The river flows west of the city swinging southward to El Paso, Texas. Twelve miles east of the city, the rim of the Sandia Mountains stands 10,678 feet above the valley floor. A tableland or "mesa" slopes gradually from the base of the mountains to the river valley which is from two to three miles wide with a floor of hard clay, sand and gravel. Many sandy arroyos or dry stream beds cut through the gravelly soil of the mesa.

Precipitation in the valley averages 8 inches a year, which is sufficient to support little more than a desert flora, while in the mountains it is greater, probably 32.6 inches a year, sufficient to support a mixed forest. The forest floors in the mountains contain much humus and retain the moisture, resulting in heavy growths of timber, particularly on the east slope of the Sandias on the far side from the city. The mesa soil contains no humus, consequently has no capacity for holding moisture.

Most of the grasses, weeds and trees involved in the hay-fever problem in and around Albuquerque were found accompanying the irrigation systems, in the borrow ditches along the highways which collect the rain draining from the pavements, and in areas where the water table has been brought close to the surface by irrigation ditches or the river.

From The Maytag Research Laboratories of the Southwestern Presbyterian Sanatorium, Albuquerque, New Mexico.

TABLE I. HAY-FEVER PLANTS OF ALBUQUERQUE, NEW MEXICO

Field Observations—1945

Plants listed as to season and major and minor causes of hay fever

SPRING		SUMMER		FALL		WINTER	
MAJOR	MINOR	MAJOR	MINOR	MAJOR	MINOR	MAJOR	MINOR
Trees—Early and late flowering species		*Trees*—Late flowering species		*Trees*		*Trees*—Early flowering species	
Juniper	Elm		Pine				
Cottonwood	Tamarisk		Locust		none		Elm
	Oak		Mulberry				
	Ash		Tree of heaven				
	Maple		Tamarisk				
	Pine						
	Locust						
	Catalpa						
Grasses		*Grasses*		*Grasses*		*Grasses*	
Bermuda	Johnson	Bermuda	Blue	Bermuda	Johnson		
	Brome		Johnson		Finger		none
	Blue		Western June		Grama		
			Salt sacatone		Salt sacatone		
Weeds		*Weeds*		*Weeds*		*Weeds*	
	Plantain	Russian thistle	Plantain	Russian thistle	Wingscale		
			Lambs quarters	Pigweed	Amaranths		Russian thistle (only slight)
			Amaranths	False ragweed	Burning bush		
			Burning bush		Redsage		
			Redsage		Pasturesage		
			Shadescale		Bur ragweed		
			Pasture sage		Sagebrush		
			False ragweed		Cocklebur		
					Lambs quarters		

The valley has a comparatively low mean annual range of temperature (55.6°F.) and a daily high range. Over a period of 50 years the average daily maximum temperature for June was 88.2°F. and the average minimum 58°F., giving a range of 30.2°F. The average date of the first killing frost is October 28 and the last, April 13. This gives an average of 198 frost-free days which tends to produce a long pollinating period.

Albuquerque is in the "Sunshine State." The annual average amount of sunshine is 76 per cent. As a result of the regular sequence of the climatic influence the plants flower and fruit with clock-like regularity.

Wind is another factor having effect on the production and distribution of pollen. Wind increases the evaporation of moisture from the soil and plants, consequently the spring season which is the windiest is the driest. The prevailing winds blowing to Albuquerque area from the south and southwest, sweep over broad expanses of arid caprock mesas, spotted with scrubby juniper trees, and carry away from the city the pollens of the trees and plants which grow in the more verdant high altitudes of the mountains. Because high winds aid in the dissemination of pollen, the pollen counts taken during the months of March, April and May were the highest for the year. However, the species of pollen found were of little importance in hay fever.

Two-thirds of the area of New Mexico is representative of the Upper Sonoran zone, and comprises plains, and foothill country ranging in elevation from 4,500-7,500 feet. This is the zone of junipers, nut pine and blue grama grass. This mesa formation is characterized by low rainfall, and sparse vegetation consisting chiefly of desert shrubs (mostly composites), yuccas and short grasses.

The Transition zone covers the greater part of the Sandia mountains. It is a wide and continuous zone at approximately 7,500-9,500 feet elevation. This is the zone of the principal timber trees of the state.

The methods followed in making this study were essentially those of the average pollen survey. We are primarily interested in the anemophilous plants, and their pollen in the atmosphere. Four stations were established, and for each, the hay fever plants were listed, within a radius of 100 feet to 5 miles, their time of flowering noted, and samples of their pollen collected for making reference slides. These collecting and field stations were distributed in the city as follows: Station Number 1, State Health Laboratory, University of New Mexico, exposure 15 feet above ground, and known as the Heights District; Station Number 2, Maytag Research Laboratory, exposure 40 feet above ground, and representing the beginning of the downtown section; Station Number 3, United States Weather Bureau, Albuquerque Airport, exposure 30 feet above ground, covering the flat mesa area; Station Number 4, Rio Grande Boulevard near Old Town, exposure 4 feet above ground, representing the river area.

The gravity method for collecting pollen was used. The adhesive on

the microscope slides was glycerine-jelly with methylgreen. Each slide was kept in an exposed horizontal position with no protective shelter for twenty-four hours before being removed and studied. Throughout this study, the method of counting pollen as outlined by Dahl and Ellis[1] was used. It is called, "The Unit Area Basis," and represents the most practical standard. It is the number of pollen grains per square centimeter of surface of the exposed microscope slide determined either by direct observation or by derivation from the number of grains counted in 25 systematically distributed microscopic fields (low power, 100X). The latter calculation may be made as follows:

> Area of 1 microscopic field (low power) expressed in sq. mm. x 25 = total area examined (in sq. mm.).

The monthly values stated are the average of data collected at the four stations, graphically presented as a total pollen count. At all times, plants were collected and identified, and correlated with the pollen counts. The data of these stations varied, but it is assumed that the average of observation at these four localities represents average conditions prevailing in Albuquerque and environs.

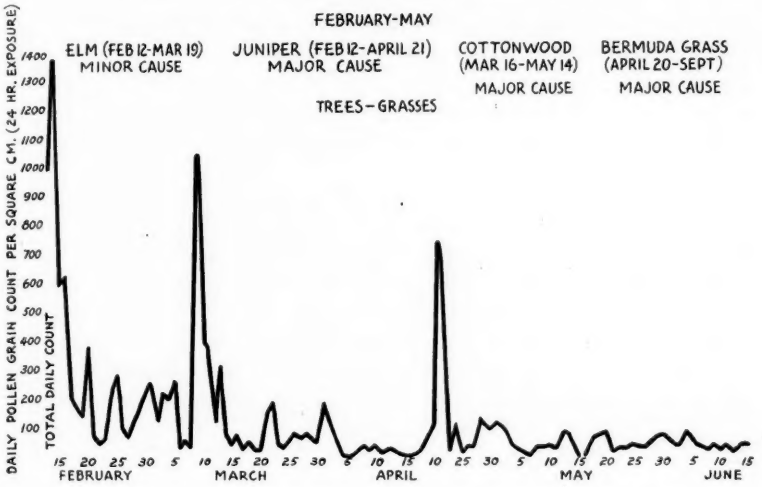
Each month is considered separately as a chronological record of the hay-fever plants and analyzed as to the species of pollen making up the total count for that particular month. As the survey was started in the middle of February, we have no data on the pollen counts for the first six weeks of the year. However, depending upon our study of the trees and climatic factors, there was a slight possibility during that period of early spring trees pollinating, such as the elm and cedar*. Both American elm and Chinese elm pollinated profusely in February. The Chinese elm is a widely planted shade and ornamental tree in and around the city and accounts for the high pollen count of this period; but elm pollen is only a minor factor in clinical hay fever. There are a number of species of junipers growing around Albuquerque. However, the total pollen count for the junipers was not high during the month.

During the month of February our data revealed a close correlation between meteorological factors and the daily pollen count, with one exception. Warm days during early spring speeded up pollen production. High winds aided its dissemination. On cold days the count was noticeably low, on warm days high. Elms continued pollinating all through March and into April, along with juniper, Arizona cypress and arbor vitae. Juniper (J. monosperma, J. scopalarius) was the most abundant plant pollinating in March. Field studies revealed that other trees beginning to pollinate were ash, cottonwood and willow. Pollen identification was difficult but juniper was found on the slides from the 9th of March throughout the month. Cottonwood pollen was first observed on the slides about March 16, increasing as the season progressed.

*In our 1946 pollen counts, February 19 was the onset of tree pollination.

As the meteorological factors became more constant in March, they showed less influence on the total pollen count. It was noted that weather factors as a whole (other than wind velocity, perhaps) had less and less effect on pollen dissemination as the summer approached.

CHART I. SPRING AND SUMMER HAY-FEVER SEASON



April brought severe hay fever in Albuquerque, and cottonwood was the primary offending pollen, although grasses and weeds began flowering during the month. Rising temperatures and spring winds combined to produce and disseminate the pollen.

The cottonwoods continued pollinating throughout April, and accounted for the majority of the pollen, with the highest daily count on the 21st at Station Number 1. The counts in the valley were lower, and the anthesis somewhat later than at the stations higher up in the mesa, with the exception of Station Number 4, which fitted in with the retarded pollination of some species in the valley due to the temperature inversion. Some juniper pollen was still in the air, but of no clinical moment. The Chinese and American elm had undoubtedly completed pollination, although an occasional grain was found now and then. Ash, boxelder and willow pollinated in limited amount throughout the entire month, but none of their pollen was trapped on the slides. It played no part in the tree hay fever here.

The grasses began flowering in mid-April complicating the work of identification of the pollen grains on our slides. It was almost impossible to identify those of grass without going into the field and making reference slides directly from the plants. This work had to be continued until

the end of the hay-fever season in October to make certain the identification of pollen from an increasing number of plants. Blue grass or June grass (*Poa pratensis*) began flowering about the 15th of April, and Bermuda grass (*Cynodon dactylon*) about the 20th. These are not range grasses, but are widely planted in Albuquerque lawns. Blue grass and Bermuda grass make up most of the lawns in the city and, of all the hay fever grasses, Bermuda is considered the greatest offender.

In April, many herbaceous flowers and shrubs, both cultivated and wild, made their appearance, also the flowering of oaks. The only oaks near Albuquerque are scrub oaks (Quercus gambelii) in the foothills of the Sandias, and while they probably were pollinating, none of their pollen was observed on the slides, probably because the prevailing winds carried it away from the city.

Among the weeds, English plantain (*Plantago lanceolata*), which is considered to be of some importance as an irritant, began pollinating during the last week in April. Again, as with the grasses, there was pollen from the weeds which was not recognized, and it was necessary to go into the field to make reference slides.

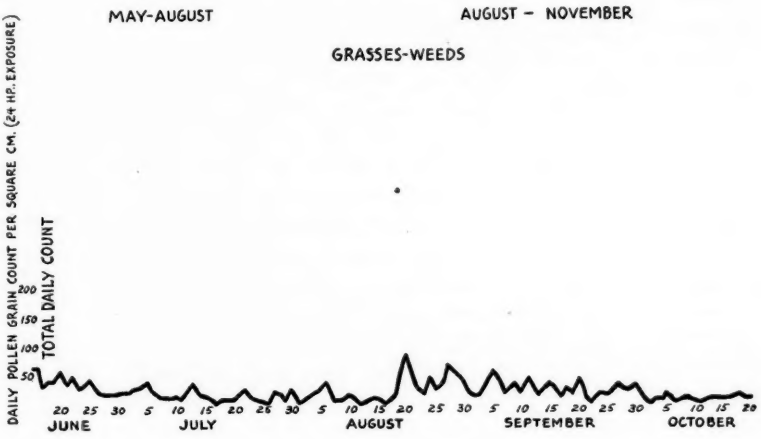
Rain and cold weather showed their usual effect in limiting pollination early in April, while warmer temperatures and winds which came later in the month aided both the production and dissemination of the pollen. The pollen count was low for the first few weeks of April, gradually rising, reaching its peak on the 21st of the month, when temperatures and wind velocity were high.

Compared with the preceding months, the total pollen count for the month of May was very low (1289) although there was a greater diversity of species. This period marks the end of the tree season, and the beginning of that of the summer pollinating plants. Trees are essentially early flowering plants, and it should be noted that they are the only species flowering before the average date of the last killing frost (April 13). The first plants to flower after this date are the early grasses such as Bermuda and Johnson grass, which might be considered indeterminate plants because of their long period of flowering.

While May is a transition period between the flowering of late spring and early summer plants, it is nevertheless marked with a diversity of pollen species resulting in difficulty of microscopic identification. We found grasses and weeds appearing in abundance. From then on they constituted the chief source of annoyance to the hay-fever sufferer. This was true especially of Bermuda grass, which flowered profusely during the whole month and continued all summer into the fall season. Other grasses such as June grass, Johnson grass, brome and perennial rye grasses were flowering, but these were of minor importance. Weeds, as a group generally are considered serious offenders. Pigweed (*Amaranthus retroflexus*), observed the last week of May, continued to flower until early fall. Lambsquarters also was noted at this period but not

in abundance. Russian thistle (*Salsola pestifer*), which is the most abundant and worst offender, began flowering at the end of May, and continued until a late hard killing frost. Plantain or buckhorn (*Plantago lanceolata*), while not very abundant, was found in flower on most lawns

CHART II. SUMMER AND FALL HAY-FEVER SEASON



throughout the month and continued to flower all summer. As the summer progressed, the diversity of pollen species increased.

June found the pollen count still declining (1108) although there was a larger variety of plants in flower at this time than at any other. The pollen count was uniformly low for July (497), so that this month is considered to be a continuation of the general summer hay-fever season. *Kochia scoparia* and *Kochia americana* were observed in the field. These are not very abundant, but have wide and spotty distribution over the city. No new pollens were listed for June, and none of the species pollinating earlier had ceased flowering.

The months of May, June and July may be considered together as the summer hay-fever season, with grasses and weeds the chief source of annoyance to the hay-fever sufferer. While the pollen count is low for this season, comparatively speaking, the species are of much greater toxicity. The chief offenders are Bermuda grass, Russian thistle and plantain.

The total pollen count in August (692) was about one third greater than that of the previous month, probably because of the beginning of what might be termed the fall hay-fever season, with the appearance of several new species, such as the sagebrushes, ragweeds and late flowering grasses. The sagebrushes (*Artemisia*) probably constituted the most important group of hay-fever plants next to the ragweeds and pos-

sibly even the grasses. Fortunately, the sagebrushes do not occur in great abundance around Albuquerque. Both the false ragweeds (*Franseria*) and the true ragweeds (*Ambrosia*) made their appearance in August. Some workers have found the pollens of the different species of *Ambrosia* to inter-react more or less perfectly, so that sensitization to that of one of them implies more or less sensitization to that of the others. Therefore, while our ragweeds are not profuse, they are considered to be of some importance.

The September pollen count was slightly higher than that of August, but from September 20 it decreased gradually to zero. September marked the end of the flowering period for some of the hay-fever species, such as plantain, burweed, pigweed and Johnson grass. However, others, such as Russian thistle, common sunflower, the false and true ragweeds, cockleburs, burning bush, redsage, several sagebrushes, as well as many composites and late flowering grasses continued their flowering all month.

There was a very pronounced drop in the total pollen count for the month of October (107), due in part to the precociousness of the season, as well as to the first killing frost of the year which occurred October 28, 1945. After this killing frost the weather became colder and very few plants survived. Only Russian thistle, Bermuda grass, a few sagebrush species and ragweed were observed after the last week in October, and these only in the more favored places. No new species made their appearance this month. The end of October terminated the fall hay-fever season bringing freedom from suffering for many hay-fever patients.

DISCUSSION-SUMMARY

Plants in the temperate climates show a marked tendency to flower and fruit only at certain periods of the year, depending on the length of day. The date of flowering in any locality, is very constant, especially in a climate as equable as that in Albuquerque, where meteorological factors vary but slightly.

After the first killing frost occurring about October 28, it was noticed that only a few species survived for a short time, and these only in warm and protected places; they had disappeared by November 7. Before the last killing frost of the spring, which is about April 13, the only species flowering were the trees which are hardy, such as the elm, and considered a minor offender in hay fever. The average frost period between these two dates is 167 days, and can be considered of no importance in hay-fever management. It is the frost-free period of 198 days, from April 13 to October 28, which constitutes Albuquerque's major hay-fever season.

The Spring Season.—From about February 12 to May 7, divided into early spring and late spring by the vernal equinox, March 21. The chief

(Continued on Page 57)

Editorial

The opinions expressed by the writers of editorials in the ANNALS *are individual and do not necessarily represent the group opinion of the Board or of the College.*

CURRENT COMMENT ON ANTIHISTAMINE EFFECT

Recent experiments, designed initially to study the antihistaminic effect of pyribenzamine and benadryl, by Mayer and Brousseau, bring into sharp focus the inadequacy of the histamine theory of anaphylaxis. These investigators studied histamine poisoning in the mouse with previous administration of pyribenzamine and of benadryl. We quote from their paper:†

"If antihistaminic substances such as pyribenzamine or benadryl were given in subcutaneous injections of 10 or 25 mg. per kg. body weight fifteen minutes before the histamine injection, the toxicity of histamine was not decreased, as is usually the case with guinea pigs or dogs, but, on the contrary, was strongly enhanced. . . . Histamine phosphate alone in a dose of 375 mg. per kg. body weight was lethal for ten out of twenty-three mice (43 per cent). In combination with 25 mg. per kg. pyribenzamine, the same dose of 375 mg. of histamine killed sixteen out of sixteen mice (100 per cent), and in combination with 25 mg. per kg. benadryl, ten out of ten mice (100 per cent). . . . The dose of 25 mg. per kg. pyribenzamine, or benadryl is nontoxic for mice. . . .

"The results indicate that the increase in toxicity of histamine is proportional to the dose of pyribenzamine or benadryl previously injected. These surprising results indicate that pyribenzamine or benadryl, which strongly and specifically counteract and neutralize histamine in guinea pigs and dogs, are definite synergists of histamine in mice."

Somewhat contrary were the results with pyribenzamine and benadryl in anaphylaxis in mice, although no case was completely freed of all shock symptoms, even with high doses of pyribenzamine. Some protection was observed against convulsions and death. These experiments again emphasize the importance of obtaining quantitative data in man based upon a concept of clinical pharmacology, even though the authors emphasize that in the mouse the antihistaminic substances which they use were acting upon unusual systems. Certainly the pharmacological responses of man cannot be directly compared with those of laboratory animals. Particularly is this true where emotional factors influence the course of the disease. In view of the data of Mayer and Brousseau, it is not clear why it is desirable to emphasize the antihistaminic effects of benadryl and pyribenzamine rather than the depressive action.

H.A.A.

* * *

Since the above was written, it has come to our notice that *Science,* in the December 6, 1946, issue, contains an item describing an exhibit of the

†Mayer, R. L., and Brousseau, D.: Proc. Exper. Biol. & Med., 63:187, 1946.

Ciba Pharmaceutical Products, Inc., in which Pyribenzamine Hydrochloride was featured as follows:

"The featured product around which the exhibit is built is Pyribenzamine Hydrochloride. This preparation is a new antihistaminic compound of very high efficacy in the treatment of various types of allergy. Pyribenzamine is a synthetic drug, effective by mouth, and is therefore made available in the form of oral tablets. Its greatest success has been achieved in the treatment of seasonal allergic rhinitis (hay fever) and urticaria (hives). In these two conditions relief is obtained in approximately 85 to 95 per cent of cases. In bronchial asthma and nonseasonal allergic rhinitis the success rate is not quite as high but still remains impressive. Other and more rare forms of allergy are benefited in greater or lesser degree. Fortunately, serious undesirable side reactions from this drug are extremely rare. The exhibit depicts pictorially the dramatic effects of Pyribenzamine both in the laboratory animal and in the human subject."

There is accumulating evidence that these statistics are not based upon the experience of allergists as a whole. There is no doubt that the discovery of Pyribenzamine Hydrochloride is a step in the right direction, and Doctor Mayer is to be congratulated upon his contribution to its discovery. It will take another hay-fever season or two before any accurate evaluation can be made.

F.W.W.

THE VETERANS ADMINISTRATION AND ALLERGY

There has been considerable dissatisfaction expressed by members of the College concerning the way the Veterans Administration has been recognizing the importance of care of allergic veterans.

A uniform and adequate fee schedule for the care of veterans suffering from allergy is highly desirable. We understand that this matter is now being worked out in Washington by the Veterans Administration. Each state seems to have its own schedule of fees, based upon the State Committees on Medical Economics. This has led to absurd suggestions; for instance, in one state it is proposed that the asthmatic veteran be charged twenty-five dollars for inhalants and twenty-five dollars for food tests, which is another way of saying fifty dollars. Every asthmatic is entitled to an exhaustive investigation, and a uniform policy for the study of the allergic veteran should be in operation soon.

It is very evident, also, that the Veterans Administration, when appointing the Branch Section Chiefs, has openly showed favoritism toward one allergy society.

During World War II there was considerable evidence that personal prejudice and the opinions of one or two distinguished laymen entered into other branches of the Government when dealing with allergy. An example was the sudden closing of the Central Allergy Laboratories of the Fourth Corps Area under Col. Sanford French, which made allergenic

extracts. This station supplied allergenic extracts for many officers in charge of allergy stations all over the United States as well as the Pacific area, thus saving thousands of dollars for the government. These abuses call for a Congressional investigation in the near future.

Veterans are writing to the College secretary frequently, because of the attitude of the Veterans Administration toward compensation for allergies acquired while in the services. Some of these letters would make very interesting reading if presented before an investigation committee appointed by Congress. F.W.W.

Hay-Fever Plants of Albuquerque, New Mexico

(Continued from Page 54)

offenders are juniper, cottonwood and Bermuda grass in their respective pollinating periods, with some overlapping.

The Summer Season.—From about May 7 to August 7, divided into early and late summer by the summer solstice, June 21. While the pollen count, comparatively speaking, is low at this time of the year, toxic hay-fever plants are more profuse. The chief offenders are Bermuda grass, Russian thistle and plantain.

The Fall Season.—From about August 7 to November 7, divided into early and late fall by the autumnal equinox, September 21. Russian thistle, pigweed and western ragweed are the chief offenders.

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A.M.

8:00- 9:00 Registration

9:00- 9:10 Address of Welcome
HARRY R. WAHL, M.D., Dean, School of Medicine, University of Kansas.

9:10-10:00 Chemistry and Allergy
RUSSELL C. MILLS, Ph.D., Assistant Professor of Biochemistry, School of Medicine, University of Kansas.

10:00-11:00 Physiological Aspects of Allergy
KENNETH E. JOCHIM, Ph.D., Professor of Physiology, School of Medicine, University of Kansas.

11:00-12:00 Antigen-Antibodies as Related to Allergy
NOBLE P. SHERWOOD, Professor of Bacteriology, School of Medicine, University of Kansas.

12:00-12:15 Orientation—Chairman

P.M.

2:00- 3:00 Bacterial Allergy
FRED W. WITTICH, M.D., Minneapolis, Minnesota

3:00- 4:00 Diagnosis of Allergic Disease
M. MURRAY PESHKIN, M.D., Instructor, College of Physicians and Surgeons, Columbia University.

4:00- 5:00 Hay Fever—Diagnosis and Management in Children
ALBERT STOESSER, M.D. Clinical Professor of Pediatrics, University of Minnesota, Director of Allergy Clinics at University Hospitals and Minneapolis General Hospital.

5:00- 5:45 Hay Fever—Specific and Symptomatic Treatment
LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

Tuesday, May 6, 1947

A.M.

9:00-10:00 Botany
ROGER WODEHOUSE, Ph.D., Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, New York

10:00-11:00 Bronchial Asthma—Classification and Treatment
LEON UNGER, M.D., Associate Professor, Department of Medicine, Northwestern University Medical School, Chicago, Illinois

11:00-12:15 Histaminic Cephalgia and Migraine
BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota.

P.M.

2:00- 3:00 Bronchial Asthma in Infants and Children
M. MURRAY PESHKIN, M.D., Instructor, College of Physicians and Surgeons, Columbia University.

3:00- 4:00 Chronic Cor Pulmonale—Complications of Chronic Lung Disease
MAHLON DELP, M.D., Assistant Professor of Medicine, School of Medicine, University of Kansas.

4:00- 5:00 Allergic Rhinitis
FRENCH K. HANSEL, M.D., Associate Professor of Otolaryngology, Washington University.

5:00- 5:45 Allergic Rhinitis—Management and Treatment
W. BYRON BLACK, M.D., Kansas City, Missouri

Wednesday, May 7, 1947

A.M.

9:00-10:00 Food Allergy
ORVAL R. WITHERS, M.D., Associate Professor of Medicine, School of Medicine, University of Kansas.

10:00-11:00 Common Air Molds in Relation to Allergy
HOMER E. PRINCE, M.D., Associate Professor of Medicine, School of Medicine, Baylor University, Houston, Texas

11:00-11:30 Poison Ivy
LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

11:30-12:15 Ménière's Disease
BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota

P.M.

2:00- 3:00 Antibiotics in Allergy
EDWARD H. HASHINGER, Professor of Clinical Medicine and Director of Graduate School of Medical Education, School of Medicine, University of Kansas.

3:00- 4:00 Skin Allergy Due to Fungi
CHARLES C. DENNIE, Professor of Dermatology, School of Medicine, University of Kansas

4:00- 5:00 Dermatologic Allergy in Infancy and Early Childhood
ALBERT STOESSER, M.D., Clinical Professor of Pediatrics, University of Minnesota, Director of Allergy Clinic at University Hospital and Minneapolis General Hospital.

5:00- 5:45 Practical Management of Contact Dermatitis
R. L. SUTTON, JR., M.D., Associate Professor of Dermatology, School of Medicine, University of Kansas.

7:00-10:30 Dinner and Round-Table Discussion

Thursday, May 8, 1947

A.M.

9:00- 9:45 Physical Allergy.
CECIL KOHN, M.D., Kansas City, Missouri.

9:45-10:30 Status Asthmaticus—Treatment
ALLAN G. CAZORT, M.D., Little Rock, Arkansas

10:30-11:00 Pathology of Allergy
LEON UNGER, M.D., Associate Professor, Department of Medicine, Northwestern University Medical School, Chicago, Illinois

11:00-11:30 Gastrointestinal Allergy
ORVAL R. WITHERS, M.D., Associate Professor of Medicine, School of Medicine, University of Kansas.

11:30-12:15 Value of X-Ray in Allergy—Diagnosis and Treatment
GALEN M. TICE, Associate Professor of Roentgenology, School of Medicine, University of Kansas.

P.M.

2:00- 5:45 Laboratory and Clinical Sessions
Laboratory Session (Technique)—Asthma Clinic—Hay-Fever Clinic—Dermatology Clinic

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The fee for the course is $50.00 payable at the registration desk, University of Kansas Hospital, W. 39th St. and Rainbow Blvd., Kansas City, Kansas. Applications for the course and for hotel reservations should be placed with the chairman of the Program Committee, Orval R. Withers, M.D., 1418 Bryant Building, Kansas City, Missouri. Doctor Withers has made arrangements for hotel reservations at the following three hotels: Bellerive, 214 East Armour; LaSalle Apartment Hotel, 922 Linwood; and Ambassador Hotel, 3560 Broadway. Only twin bedrooms are available.

All physicians interested in Allergy are invited to take this course.

Progress in Allergy

PEDIATRIC ALLERGY

A Critical Review of Recent Literature

JEROME GLASER, M.D., F.A.C.A.
Rochester, New York

BRONCHIAL ASTHMA

The relationship of the thymus gland to dyspnea in infancy and childhood continues to puzzle pediatricians, and the question cannot yet be regarded as settled. Possibly Carr[10] has made a useful contribution to this subject in reporting a new descriptive term which denotes a disease entity which he states is frequently responsible for strangulation in the young, namely, "status thymico-asthmaticus." Under this heading is presented a series of cases occurring in widely varying age groups, in which death has occurred from asphyxia and in whom the thymus is enlarged. This enlargement is of lesser degree than that seen in patients who have died of acute tracheal compression from an enlarged thymus, and associated with it is a hyperplasia of the lymphoid system which, instead of being generalized, is limited largely to the bronchi and bronchioles. Because the lymphocytic infiltration is in the submucosa and among the muscle fibrils, as well as peribronchial, the term asthmaticus is included. This picture cytologically resembles a developing or existing asthma, and the clinical course is differentiated with difficulty from true asthma, except for the single but very important fact that the status thymico-asthmaticus group shows no beneficial response to the injection of epinephrine. The author states that the pathological picture resembles that described by Waldbott[91] in his report of two infants apparently dying from asthma. Because of the pathological changes, Waldbott stated at that time that he thought it possible that thymic death and death from allergic shock might be equivalent.

Flensborg[30] has attempted to discover the chances for recovery from bronchial asthma in infancy when treated by the usual measures employed in Denmark previous to the introduction of specific therapy in 1943. The study was made on the basis of satisfactory replies to 298 questionnaires. Of these, there were 190 boys and 108 girls. In the great majority, 197 out of 298, the attacks commenced before the age of five years. The usual ages of onset were the second and third years. The asthma was regarded as having ceased in those patients who had no attacks for at least one year. In most of the boys the asthma ceased between twelve and fifteen years of age. With the girls the attacks usually ceased between nine and twelve years.

Among the 298 children were 100 who constantly suffered from attacks and who, at the time of the inquiry, were more than fifteen years old, besides sixteen children whose attacks of asthma had ceased after the age of fifteen. Of these 116 patients, thirty-nine, or about a third, reported that they had chosen a special profession on account of their asthma. About 40 per cent of the cases of asthma starting in infancy recovered spontaneously or under the treatment employed. Infantile asthma occurred much more frequently in boys than in girls. Of the 298 children, school attendance was seriously interfered with in 139, or almost half of the cases. Among

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116 children whose attacks had ceased at the time of inquiry the average duration of the disease had been 7.4 years. In the case of the boys, the average was 7.7 years; for the girls, 6.9 years.

The following explanations were given in the questionnaires as probable causes of cessation of the asthma:

Patient's removal to another place in the country, or another residence in the same town	31
No attacks since patient's discharge from hospital	10
Sanitation of lodgings or room	9
Spray treatment	3
Residence at health resort or sanatorium for children	2
Sport and open air environment	2
Dietary treatment	2
Corset treatment	2
Respiratory gymnastics	1
Vaccination against "colds"	1
Attacks ceased after whooping cough	1
Attacks ceased after rheumatic fever	1
No cause known	49
No information	6
Total	120

Melamed[57] has contributed some interesting statistical figures on the occurrence of bronchial asthma in children in Palestine. The difficulty of securing such statistics is the same in Palestine as it is elsewhere, consisting chiefly of (1) the lack of a central institution to which all cases of bronchial asthma are reported, (2) the lack of long-continued observations in individual cases, and (3) the difficulties of diagnosis, particularly at the onset of bronchial asthma in childhood. Confusion is also caused by the fact that some authorities consider asthmatic bronchitis as a form of bronchial asthma. For statistical purposes, the author attempted to differentiate between these two conditions. The author's material consisted of the children in the Sick Fund of the southeastern district of Tel-Aviv for the year beginning July 1, 1943. The Sick Fund numbered 1,400 children the first year of the study. The number of asthmatic children under seven years of age at that time was sixty-nine. Of these, twenty-three had bronchial asthma and forty-six had asthmatic bronchitis. In the second year of the study, which began July 1, 1944, there were 1,600 children. Of these, among the children seven years of age or less there were 105 with asthma; thirty-seven had bronchial asthma, and sixty-eight had asthmatic bronchitis. The average percentages of children in the two groups, 5 per cent for the first year of the study and 6.5 per cent for the second year of the study, are quite close. It is interesting that in the total series, the sex distribution (50.5 per cent for females and 49.5 per cent for males) was almost identical. This is not in accordance with the figures presented above by Flensborg[30] from Denmark or the previously published figures by Bray[6] from England, both of which showed a marked preponderance of asthma in boys. It is interesting that about twice as many cases of asthma occurred in children with fair complexions (66 per cent) as in dark-skinned children (34 per cent). The average onset of the asthma was between four and six years of age. The majority of the asthmatic attacks occurred during September, October, and November. The month with the least number of attacks was August.

COMPLICATIONS OF BRONCHIAL ASTHMA

A case of probable death from asthma was reported from the Children's Memorial Hospital in Chicago.[12] The child, a boy twenty-two months of age, was first seen at the age of eleven months because of asthmatic bronchitis which followed an upper respiratory tract infection at the age of eight and one-half months.

A running nose and intermittent cough had persisted since the initial attack. The child was relieved after a few days of symptomatic treatment and was readmitted to the hospital a month later for bronchoscopy. The findings were normal. At the age of fifteen months, bronchial asthma was diagnosed and he was studied with negative results. The child was then taken to Alabama, where his condition remained unchanged, and he received numerous injections of adrenalin without relief. He was restudied from the standpoint of bronchial asthma by the same allergist (Dr. Leon Unger) at the age of eighteen months, again with negative results.

The boy's final admission was at the age of twenty-two months. Two days before admission he had had a running nose and on the day before, severe asthmatic attacks had started. Adrenalin had been given repeatedly without relief. The only other medication the child had received had been atropine drops three times a week for strabismus. The child was cyanotic and comatose on admission and critically ill. His rectal temperature was 100.6°. There were numerous wheezes and rhonchi over both lungs. A roentgenogram of the chest was normal. He responded rather well to parenteral aminophyllin, adrenalin in oil, and oxygen. That night he again became worse, and in spite of a variety of therapeutic measures, including parenteral fluids, penicillin and coramine, his temperature rose to 107.2° F. and dropped to 101.6° F. three hours later, the patient dying shortly thereafter.

At autopsy, 100 to 150 c.c. of sterile fluid of unknown origin was found in each pleural cavity. The branches of the bronchial tree were entirely occluded with a thick, light-green, tenacious mucus which by smear showed numerous eosinophil cells. On culture, B. coli was isolated. The final anatomical diagnosis was marked mucopurulent bronchitis and bronchiolitis; asthma (clinical); bilateral hemothorax; foci of atelectasis; and compensatory emphysema; foci of pulmonary edema. As Unger suggested in discussion of this case, the child might possibly have been helped by bronchoscopy in his terminal illness, but his condition was considered too critical to attempt this.

A death from asthma in a thirteen-year-old boy has been reported by Pedrera.[62] The onset of the attack was sudden and severe. He did not respond to therapy and died a few hours after the onset. There was no necropsy. The family history was positive for allergy, in that the father was known to be sensitive to fish and a younger brother had died of anaphylactic shock following the administration of tetanus antitoxin. The present patient's asthma had started at the age of six years and had gradually increased in severity. At the age of twelve years, he was studied from the allergic standpoint and did very well on the therapy instituted. After he had been free from attacks for two months, he was not seen again until his terminal illness. The author briefly discusses the mechanism of death from asthma which he regards as not yet having been satisfactorily explained. He believes that dehydration and disturbances of acid-base equilibrium may play a large part.

A case of mediastinal and subcutaneous emphysema was described in an asthmatic girl, five years of age, at the Children's Memorial Hospital of Chicago.[11] She had been referred with a diagnosis of virus pneumonia because of the numerous râles which had been heard on auscultation of the chest. On more complete physical examination and x-ray investigation, the true diagnosis was discovered. The child made an uneventful recovery. In the discussion, the subject of emphysema of this nature is beautifully reviewed. The characteristic x-ray finding in mediastinal emphysema is the elevation of the mediastinal pleura from the mediastinum and pericardium, producing a rather characteristic and unique line on one or both sides of the mediastinal shadow.

On the left, this line is commonly visible above the pulmonary vessels. The condition is produced by the escape of air from ruptured alevoli. This travels along the course of the vessels into the mediastinum. The most persistent finding is a crunch-

ing, bubbling sound heard over the precordium during the cardiac contractions. This is sometimes mistaken for air in the pericardial cavity. Since cardiac tamponade with subsequent death may result from the increased mediastinal pressure due to mediastinal emphysema, it is occasionally necessary to release the air in the mediastinum surgically. This may be done by needle puncture, dissection through the neck, or splitting the sternum.

Pneumothorax may occasionally be produced by the rupture of an overdistended mediastinal wall, rather than by a pleural defect or a ruptured emphysematous bleb. Subcutaneous emphysema as a result of bronchial asthma in children is not common, only seven cases having been reported up to 1941 in children under ten years of age.

Derbes and Engelhardt[19] have summarized their studies, previously reviewed in these columns,[34] on the influence of bronchial asthma on the heart in childhood, with the statement that their varied data tends to show that in children uncomplicated bronchial asthma is not a factor in the production of heart disease.

CONDITIONS SIMULATING BRONCHIAL ASTHMA

Acute and chronic respiratory disturbances in which the clinical manifestation is an expiratory type of dyspnea associated with a generalized emphysema, are not uncommon during the first few years of life. This fact is discussed by Nelson and Smith.[58] Respiratory obstruction in these instances is mostly in the distal or smaller bronchioles, and, clinically, such diagnostic terms are employed as bronchiolitis, capillary bronchitis, pneumonitis, interstitial pneumonia, and sometimes aspiration pneumonia. There is usually both inspiratory and expiratory obstruction but the difficulty in expiring the air is more prominent, and air is trapped in the alveoli, producing emphysema. Clinically, there are certain similarities to asthma, but in contrast to the usual relatively short duration and self-limited course of the average attack of asthma, even the acute forms of obstructive emphysema in infants tend to persist for a week or so and often much longer. Furthermore, while asthma is perhaps the most frequent cause of obstructive emphysema in older children, it is relatively uncommon in the first year or two of life when the conditions discussed characteristically occur. Producing this type of respiratory disturbance, the authors give illustrative cases including aspiration of amniotic fluid during birth, cystic fibrosis of the pancreas, atypical bronchopneumonia, laryngotracheobronchitis, miliary tuberculosis, aspiration of zinc stearate powder, and chronic passive congestion secondary to congenital heart disease.

One of the above conditions, bronchiolitis, in infants is discussed by Pratt[65] in considerable detail. As other terms for this condition, he mentions bronchitis, capillary bronchitis, asthmatic bronchitis, and bronchopneumonia. Acute bronchiolitis occurs most frequently in infants three to eighteen months of age. It is a syndrome characterized by rapid, labored respiration, audible wheezing, prostration, cyanosis, pulmonary emphysema, and signs of exudate in the smaller air passages, leading to obstructive dyspnea and terminal asphyxiation. It generally begins with nasal discharge followed by a slight cough and an increased respiratory rate. The breathing becomes noisy and is described as "wheezing" or "rattling in the chest." It may be accompanied by diarrhea or vomiting, and there is usually moderate fever. As the condition becomes worse, breathing becomes more difficult and there is often audible wheezing. This occurs in about one-third of the subjects and is a symptom which leads to confusion of this condition with bronchial asthma. Pratt makes the interesting observation that allergy or chronic respiratory tract infection is not more frequent than normal in the families of these patients. However, he does not mention eosinophil smears of the nasal or pharyngeal mucus, and there is no mention of blood counts with reference to eosinophilia.

As the condition progresses, the character of the respirations becomes distinctive. The symptoms are those of obstructive emphysema. The accessory muscles of

respiration are used; the thoracic cage is fixed in a position of inspiration. The chest is hyperresonant to percussion; the breath sounds during expiration are moderately prolonged. Wheezing may be heard on auscultation of the chest in about half the cases. The most distinctive feature on auscultation is the presence of many râles throughout the lungs. The breath sounds vary considerably in character and may resemble bronchial asthma. The roentgenograms show certain characteristic changes[60]: emphysema involving all portions of the lungs; bulging of the emphysematous tissue into the interspaces is a prominent feature. There is increase in bronchovesicular markings and varying degrees of peribronchial infiltration, with small patches of pneumonic consolidation or atelectasis toward the base. There is irregularity of aeration with multiple small areas of emphysema surrounded by normal or partially atelectatic lung tissue. The mediastinum is not displaced. The diaphragm is depressed and the thoracic cage is fixed in the position of extreme inspiration.

A small proportion of the infants, although seriously ill, make a rapid recovery within a day or two. Only rarely does acute bronchiolitis progress into a protracted bronchopneumonia. Such an occurrence should lead one to suspect the presence of some underlying disturbance, such as pancreatic fibrosis or the aspiration of a foreign body.

The treatment of the disease is with measures appropriate for an acute pulmonary infection. Sulfadiazine is recommended. Cool, moist air with a relative humidity of 95 to 100 per cent is said to be better than steam. For difficult breathing, aminophyllin in doses of .006 grams per kilogram (1/20 of a grain per pound), combined with 2 c.c. per kilogram (1 c.c. per lb.) of a 50 per cent dextrose solution, is given slowly intravenously. This is repeated every six to eight hours if effective. It should be discontinued if there is any tendency towards thickening of the secretions. Oxygen is useful, and the author recommends a nasal catheter or an open top box with cool moist air. For circulatory collapse, caffeine sodium benzoate in doses of 0.03 to 0.13 grams (1/2 to 2 grains), or metrazol, 0.25 or 0.5 c.c. (4 to 8 minims), can be used. For abdominal distention, pitressin, 0.5 to 1.5 units, is given intramuscularly, or prostigmin methylsulphate, 0.25 to 1 c.c. of a 1:4000 solution, intramuscularly or subcutaneously.

Adenoid bronchosinusitis in infants and children is described by Clifford, Neuhauser, and Ferguson.[14] This develops commonly as a complication of an upper respiratory infection. The history is that the patient has never fully recovered from an original "cold" acquired some months previously. The infected adenoid tissue and nasal sinuses produce a purulent discharge which obstructs the nasal passages and descends into the trachea and bronchi. In time, this postnasal dripping may penetrate the finer bronchi and cause profuse peribronchial infection. The main symptoms are persistent nasal discharge, mouth breathing, snoring at night, postnasal drip at night causing cough, and profuse nasal discharge during the day. An attack of asthma may be precipitated, or the disease may be complicated by capillary bronchitis or pneumonia.

Adenoid bronchosinusitis is characterized by periods of exacerbations and remissions. Recurrent attacks of tonsillitis, cervical adenitis and otitis media are frequent. Nearly all cases begin in September, October, or November. The patients range in age between eleven months and eight years. It is rarely seen at later ages because of the development of individual immunity, the relative increase in size of the nasal pharynx, and atrophy of lymphoid tissue, which generally takes place in adolescence. The author states that good results are obtained by a combination of chemotherapy and surgery. Although this condition is often seen in children known to be allergic, the authors do not discuss the relationship between allergy and this disease.

A condition closely related to the above has been described by Dutton and

Fuchlow[23] under the term of the "sinobronchial syndrome," which may be defined as an involvement of the sinus membranes by an infectious process of sufficient intensity to have implanted itself secondarily upon the bronchial mucous membranes by virtue of postnasal drainage. Admittedly, there may be considerable difficulty in differentiating sinus involvement due to such a chronic infection from that due to allergy. The sinobronchial syndrome may be identified as at least one factor in the production of otherwise unexplained symptoms in children apparently under adequate allergic management and for which no atopic etiology is demonstrable. The authors summarize the differential diagnosis between asthma due to atopy and asthma due to the sinobronchial syndrome as follows:

DIFFERENTIAL DIAGNOSIS

	Asthma Due to Atopy	*Asthma Due to Sinobronchial Syndrome*
1. Onset	Eczema, hay fever, asthma triad	Asthma begins with colds
2. Duration of attacks	Paroxysmal, short duration	Gradually developing, longer duration
3. Fever	Not usual	Usual
4. Response to adrenalin	Good	Poor
5. Leukocytosis	Infrequent	Frequent—moderate to high
6. Sedimentation	Very slow	Normal or rapid
7. Nasal smears	Eosinophilic	Neutrophilic
8. Bacteriology	Indifferent	Usually streptococcal pneumonia or staphylococcal
9. X-ray chest	Minimal changes	Striking changes
10. X-ray sinuses	Minimal changes	Striking changes
11. Seasonal incidence	Not seasonal or corresponds to pollen season	Winter or change of weather

The symptoms of the sinobronchial syndrome as they occur in the allergic individual are generally rhinitis, postnasal drainage, cough, wheezing, and fever. The physical findings are not strikingly different than those found in atopic asthma. Roentgen treatment is recommended and this is best carried out in the chronic phase. Generally, about 400 roentgens over the sinuses and 800 to 1,400 over the chest, in four to six daily treatments, are given. There is generally a gradual improvement of the entire condition of the patient within four to six weeks, an improvement which persists for a variable period of time up to several months or even indefinitely.

While bronchial stenosis due to syphilis has been described and the same condition caused by tuberculosis has received considerable attention, little has been written about nontuberculous bronchial stenosis. Hollinger[43] demonstrated in 1938 that bronchial inflammation can cause bronchostenosis and finally bronchiectasis. This disease has recently been reviewed by Schmidt.[75] It is characterized by a cyclic course. The attacks usually start with an irritating nonproductive cough. Chills and fever, 38.8° C. to 39.4° C. (102° F. to 103° F.), and general malaise occur, and this episode lasts on the average from two to seven days. Then, variable amounts of sputum, occasionally blood tinged, are coughed up and the symptoms are relieved. Symptom-free periods may last from three months to three years. These individuals generally have a history of antecedent pneumonia, severe tracheobronchitis, or repeated attacks of asthmatic bronchitis. Recurrent pneumonia, influenza, malaria, and brucellosis are some of the diseases commonly considered in a differential diagnosis. The attacks are due to stagnation of infected material distal to a stenosed bronchus. A local pneumonic process develops. Symptoms persist until drainage is re-established.

Bronchoscopy is the only clinical method of determining whether or not bronchial stenosis exists and is the only way in which such a lesion can be satisfactorily treated. It is wise, however, to wait two or three weeks after recovery before

attempting treatment by this procedure if there has been a recent attack. The author reviews twenty-five cases, in fifteen of which the bronchial stenosis was secondary to asthma or asthmatic bronchitis. There were a number of children in the series, the youngest of whom was six years of age. Bronchoscopic dilation produces satisfactory results in about 66 per cent of cases. In a certain number of cases the stenosis recurs and it is necessary to repeat bronchoscopic dilation. The physical and roentgenographic findings vary. In some cases, they may indicate partial atelectasis of the lower lobe of one lung although the disease may occur in the upper lobes or in the middle lobe of the right lung. In other cases, the above findings may be negative.

Apparently a very similar, if not identical, condition has been described by Leegaard[50] in Sweden, under the name "nonspecific circumscribed bronchitis." He states that the cause of condition must be (if it is really a distinct disorder) an ordinary acute, diffuse infection of the lower air passages. It is then reasonable to suppose that on a mucous membrane thus altered by inflammation there may arise more pronounced changes or an erosion, occasioned by traumatization of the diseased membrane and occurring perhaps most readily during severe coughing, or possibly due to irritation by a very minute foreign body which is afterwards removed by coughing or in some other manner. The condition probably arises frequently and is called a cold or pulmonary catarrh, and most frequently subsides spontaneously without leaving any sequellae. Acute and chronic lung diseases frequently give rise to similar bronchial changes. The most important symptoms are cough, hemoptasis, and signs of bronchial stenosis. Circumscribed lesions of the mucous membrane of the larger bronchi, with redness, edema, and considerable granulation tissue, were demonstrated on bronchoscopy. In two patients there was atelestasis of one lobe. In the majority of cases the disease subsides spontaneously, but considerable secondary changes may occasionally be produced in the lungs and bronchiectasis may result. The author describes six cases, four in women between the ages of twenty-nine and forty-one, one case in a man aged twenty-five, and another in a boy seven years of age.

Diaz-Nielson[20] has reported a case of bronchiectasis in a six-year-old boy who had been ill since the age of three years, following what was diagnosed as pneumonia. Since then, he had had almost constant cough with expectoration. The roentgenogram suggested a diagnosis of bronchiectasis. This diagnosis was confirmed by bronchography. The author believes that bronchiectasis from any cause is commonly associated with a constitutional predisposition. Although an attempt should always be made to treat the condition medically, it is potentially a surgical disease. If treated surgically, radical measures are generally advisable and are commonly successful. Lobectomy or pneumonectomy are the operations of choice but these have a mortality of 10 per cent.

BRONCHOSCOPY IN ALLERGIC PULMONARY DISEASE

It is often not realized that bronchial asthma is but one of many forms of obstructive emphysema, although it is indeed the commonest form. The differential diagnosis of bronchial asthma thus becomes a question of determining from which type of obstructive emphysema a patient is suffering. Holinger and Rigby[44] have discussed the question of bronchial obstruction in infants and children in considerable detail. The four types of valvular obstruction in bronchial asthma—by-pass, check, stop, and ball—are described. The important symptoms of bronchial obstruction, while not completely characteristic, are fairly constant. These are: cough, which may be dry and nonproductive for weeks and then suddenly be associated with hemoptasis and a foul, purulent sputum produced by superimposed infection; wheeze, commonly heard throughout the chest and loudest over the location of the obstruction; dyspnea of varying degree. Pain is not common but occasionally occurs and may be localized by the patient to the site of the foreign body.

One of the most constant physical signs in almost all cases of bronchial obstruction is the definite limitation of motion on the involved side, independent of the degree of obstruction. Tracheal obstructions due to mediastinal neoplasms not infrequently involve the esophagus as well, and consequently the child has difficulty in swallowing and regurgitates food into the trachea due to esophageal overflow. The increased positive pressure of expiration has no appreciable effect on blood flow through the thorax. However, the increased negative pressure on inspiration has definitely harmful effects, resulting in pulmonary congestion, transudation, and edema.

In summary, the authors state that physiological effects of tracheobronchial obstruction may be divided into their respiratory and cardiovascular reactions. Mild obstruction results in a dyspnea which remains compensated by reflex and physiochemical stimulation. Severe obstruction results in respiratory decompensation or anoxia. Long-standing obstruction results in pulmonary suppuration, bronchial obstruction, and bronchiectasis. The cardiovascular phenomena manifest themselves by pulmonary edema and finally circulatory failure due to rising intrathoracic negative pressures.

Lell,[52] in an exceedingly valuable bronchoscopic study of 176 children thought to be suffering from epinephrine-fast bronchial asthma, has pointed out the great value of the bronchoscope in the diagnosis and treatment of this condition. Of these patients, 130 were found to have true bronchial asthma; thirteen had a foreign body in the bronchus; in fourteen there was tracheal compression from external causes; eight had organic changes in the larynx; five had foreign bodies in the esophagus; five others had foreign bodies in the larynx; and one had a retropharyngeal abscess. Lell states that all patients examined during an attack of asthma showed changes which are fairly constant and uniform. The mucous membrane is always hemorrhagic, red, and redundant, greatly reducing the caliber of the lumen of the trachea and both main bronchi. Secretions are always present and so tenacious that they are difficult to aspirate. The classic phenomenon of collapse of the posterior tracheal wall is frequently present in children and almost always present in adults during status asthmaticus.

It is of great importance that a hypodermic injection of epinephrine be made just before bronchoscopy; the intravenous injection of aminophyllin produces the same effect. These procedures appear to cause the mucus to come out into the bronchi and trachea. In all cases, during the bronchoscopic examination, oxygen was administered through an attachment on the bronchoscope, thereby relieving the dyspnea. Lell emphasized the fact that treatment should be given as soon as possible during an attack.

Dighiero[21] has discussed the importance of bronchoscopy in the diagnosis and treatment of bronchial asthma on the basis of a study of twenty children, sixteen of whom were observed in the intervals between attacks of asthma and four during attacks. Those examined between attacks comprised three groups. In the first group, no pathological changes were visible. The mucosa was normal and there were no appreciable secretions or alterations. In the second group, there was severe congestion of the tracheal and bronchial mucosa with hypersecretion, a condition often called "allergic mucosa." The patients with these lesions of the bronchial mucosa were also sufferers from allergic rhinitis and had personal and family histories of allergy. The third group showed changes resembling chronic tracheobronchitis. The mucosa was thickened, pale, dull and covered with mucopurulent secretion. There were also bronchial changes characterized by flaccidity, loss of elasticity, and limitation of the movements of expansion and contraction. This flaccid state creates a favorable condition for emphysema.

The differential diagnosis between asthma complicated by bronchial infection and chronic tracheobronchitis with attacks of asthmatic dyspnea, can be made only by the

clinical history. In such cases it is necessary to treat the bronchial infection. The author has had good results from repeated bronchial aspirations, bronchoscopic instillation of sulfonamides, topical applications, et cetera, and, in cases where there was no great obstruction, from pulmonary nebulization with sulfonamides or iodized oil. In addition to these local measures, he advises general symptomatic treatment and such specific measures as may be necessary after the patient has been studied from the allergic standpoint. Bronchial aspiration combined with bronchial insufflation of oxygen is an emergency treatment in all cases of serious asthmatic attacks, with asphyxia and cyanosis, in which other treatment has failed.

Only four patients were studied during attacks. In all cases there was congestion and edema of the mucosa. The congestion was not equal in all instances, being more accentuated in those patients in whom the mucosal congestion was of an allergic nature. These lesions were accompanied by thick, mucoid or mucopurulent viscous secretions. There were also changes in the tracheobronchial movements, varying with the degree of dyspnea and the tonicity of the bronchial walls. Bronchoscopically, bronchial spasm was not seen, although it has been noted by others. The changes that were actually observed were sufficient to explain the dyspnea and the difficult breathing characteristic of asthmatics.

When congestive lesions of the mucosa as seen in allergic asthma prevail, the attacks start suddenly and rapidly become severe but always yield readily to epinephrine. On the other hand, when there is bronchial infection and changes in the tone and elasticity of the bronchi, the attacks are milder but much more prolonged; they respond very little, if at all, to epinephrine, and between attacks the patient is subject to wheezing, especially at night. A permanent form of asthmatic breathing finally develops.

TREATMENT OF BRONCHIAL ASTHMA

A discussion offering many practical suggestions in the management of asthmatic children has been presented by Bowen.[4] The use of the usual routine measures in the case of such children is thoroughly discussed. The uselessness of the routine removal of the tonsils and adenoids as a cure-all for nasal allergy and asthma is emphasized. In discussing the role of foods, Bowen makes the statement that he had never seen a proved case of allergy due to cane sugar. For the use of children who may be sensitive to various forms of cod liver oil, the use of Provatol (Wyeth) is recommended. In this preparation, vitamin A is supplied by carotene and vitamin D by irradiated ergosterol which is not derived from a fish source. The preparation is put up in a sesame oil base. In his experience, hyposensitization to food by hypodermic injection is a method which is not free from danger and as a routine procedure is to be condemned. Caution in the interpretation of skin tests is emphasized, and it is pointed out that tests with food give reliable information in less than 40 per cent of cases. Animal pets with fur or feathers are not to be recommended, regardless of the skin tests.

In taking the history, inquiry should be made regarding a child's hobbies. Bowen reports two cases of children who developed asthma while arranging their stamps in books. In each case LePage's glue was suspected and this was confirmed by further testing. This glue has a fish base. The adhesive on United States postage stamps is said to have a vegetable base. Glue is also used in the making of kites and model airplanes. In warning against cosmetics, it is pointed out that many of these not only contain orris root but also various cereal flours as rice, wheat, oatmeal, and corn. The importance of inquiring as to the use of previous medications, especially proprietary preparations, is discussed. These medications often contain aspirin, quinine, phenophthalin, iodine, or arsenic.

In this communication Bowen introduces the very useful term "wet sleeper." He describes the child whose forehead is always beaded with sweat shortly after retiring and whose pajama neck is wet. At times, the perspiration may be of such

degree that one wonders about nutritional inbalance or evidence of disease. Bowen states that it is this type of child who tolerates ephedrine poorly and may present the disagreeable side reactions of this drug. To avoid this he recommends the use of propadrine hydrochloride since its action is chiefly peripheral and does not have as many side reactions as ephedrine. Campbell[9] also some years ago pointed out that the allergic child is often prone to excessive perspiration. While I have not made a statistical study of this subject, from my experience in the general practice of pediatrics, I am inclined to feel that excessive perspiration is just one phase in the development of vasomotor stability as a child grows older. Generally speaking, the allergic child has less vasomotor stability than the nonallergic child and would, therefore, be expected to perspire with less provocation.

In treating with epinephrine, warning is given against using an unnecessarily large dose. In administering epinephrine in oil, one should be sure that the patient is not allergic to the preparation from which the oil base is made, as sesame oil or peanut oil. Gelatin is also sometimes used, and allergy to this may be present. Bowen has found the inhalation of 1:100 epinephrine of little value in children under six years of age. If this preparation is used, it is important that the patient be instructed to rinse the mouth in order to minimize throat dryness and gastric distress. If epinephrine by injection is used, Bowen makes the practical point that it is much less expensive for the parent to buy an ounce of this in a rubber-stoppered bottle than to obtain the preparation in ampules. Aminophyllin may be administered intravenously in children in doses of 0.24 to 0.48 grams (3-3/4 to 7½ grains) in 10 to 20 c.c. of distilled water. This should be administered very slowly over a period of ten minutes. According to Bowen, morphine should never be used in asthma.

It is important that allergic children be early immunized against diphtheria, pertussis, and tetanus. The child should also be vaccinated against smallpox if possible before he is a year of age. The question arose as to whether a vaccine prepared from virus grown in egg (chorioalantoic membrane) could be safely used in a child known to be egg sensitive. In order to discover the answer to this question, Bowen vaccinated five children who were completely intolerant to egg with such a vaccine. Four had successful takes and none of the five showed any unusual reaction. He concludes, therefore, that such material may be used routinely in vaccinating egg-sensitive children. This is true even though it has been shown that this vaccine does contain some egg protein. The reviewer would like to point out that in vaccination against smallpox, the vaccine is not commonly injected. For the prophylaxis of those conditions (yellow fever, typhus, influenza) where it is necessary to inject a vaccine-containing egg, very severe reactions may result in egg-sensitive individuals.

Bowen believes that vaccine therapy has a definite place in the treatment of certain asthmatic children. To this group belongs the child who rarely has asthma unless he has an upper respiratory infection. Bowen has found that a good stock vaccine is as satisfactory as an autogenous vaccine. Annual booster injections of pertussis vaccine should be encouraged.

As a complication of treatment by the injection of epinephrine in oil, Ratner[68] describes the case of a boy four years of age who was given 1 c.c. of Parke-Davis adrenalin in oil, the base of which is peanut oil, into the buttocks by another physician. The area of injection remained indurated and gradually over a period of three months the indurated area spread and fluctuant areas developed. The affected region was dull red in color, measuring about 7 centimeters in diameter. Infection was suspected but oleoma was diagnosed. This was removed surgically. The material showed fat globules microscopically. Oleomas, once formed, have a tendency to enlarge slowly and then gradually break down. In this particular case, Ratner † states that the boy was not sensitive to peanut oil.

† Personal communication to the author.

Prigal, Fuchs, and Schulman[67] have discussed the treatment of bronchial asthma with rectal suppositories of aminophyllin and sodium pentobarbital. The work was done in a clinic with ambulatory patients, who as a rule do not have severe asthma. The series, in addition to adults, included five children ranging in age from two to thirteen years. The results were just as good in children as in adults, perhaps better. Possibly this was due to the relatively large doses as compared with those given to adults. The dose for children was 0.25 grams of aminophyllin and 0.5 grams of pentobarbital sodium. The authors point out the obvious advantages of the rectal administration of aminophyllin in children as compared with intravenous administration. It was found that when the sodium pentobarbital was added to the aminophyllin suppository it required about one-half the time to secure the therapeutic effect as when aminophyllin was used alone. The addition of a barbiturate to aminophyllin suppositories to assist their action was described by the reviewer in the first of these communications.[33]

The authors observed that occasionally following the use of suppositories the patients complained of slight itching or burning, or cramps, or diarrhea. They state that this is due to failure to insert the suppository high enough into the rectum and that much of the difficulty may be overcome by lubricating the suppository with an anesthetic ointment. However, in my personal experience with aminophyllin suppositories, I have found that occasionally nausea and vomiting will occur from the suppositories regardless of how they are administered, and this probably represents a central reaction to the drug.

Lee,[49] in a general review of the subject of allergy in pediatrics, states that she has seen several sterile abscesses following the supposedly intramuscular injection of aminophyllin. When given too rapidly or in too large amounts intravenously, aminophyllin has produced profound shock, necessitating intravenous fluids and cardiorespiratory stimulation.

In connection with any discussion of the use of aminophyllin in childhood, the reviewer would like to point out that the limits of tolerance for adults and children with this drug have not yet been established. However, it is quite evident from clinical experience that the doses necessary to procure a favorable therapeutic effect are considerably less than what may possibly be the toxic doses.

Prigal[66] has also developed what may prove to be an exceedingly valuable addition to the armamentarium of the pediatric allergist in the treatment of bronchial asthma and pulmonary infections. He has devised an apparatus by means of which various solutions of drugs may be converted into aerosols by means of the passage of a current of steam. The apparatus used is very similar in construction to some of the devices now on the market for producing steam for croup tents. By means of this apparatus he has successfully treated asthma by aminophyllin aerosol. Prigal states that other drugs such as penicillin solutions, solutions of sulfonamides, and ammonium chloride may be converted into aerosols without loss of potency by the same method.

Under the medical supervision of Dr. M. Murray Peshkin, a project has been developed at the National Home for Jewish Children at Denver which will eventually yield much valuable information regarding the effect of climate on asthmatic children, our knowledge of which is pathetically meager.[56] For the past five years, this Home has been caring for underprivileged children suffering from acute bronchial asthma and other refractory upper respiratory diseases. The Home is located in Denver and is available to children whose families cannot afford expensive and costly private care. The children remain until the physician recommends that they be returned to their homes. In a comparatively normal environment and sharing the companionship with other children, the asthmatic child is cared for by a staff trained in child welfare and under the direct medical supervision of Dr. Harry I. Goldman.

During the child's stay at the Home, periodic examinations are made and full reports given to the referring physician and hospital clinics. The Home has a modern, well-equipped infirmary where children requiring bed care are attended by registered nurses under the supervision of the attending physician. The children are housed in attractively furnished congregate-cottages with individual bedrooms. Food of the highest quality is carefully prepared in modern kitchens and special diets are given when prescribed. The children participate in community life by attending the local schools and taking part in communal recreations. In addition to studies made during the child's stay in the Home, an equally thorough after-care program is carried out.

The circumstances of the development of this Home render its present use available only to children of the Hebrew faith. It is hoped, however, that experience gained at the Home will furnish adequate data as to whether or not it is worth while for such homes to be established in suitable areas to which any children who need such care may be sent. Should studies at the Home prove this to be desirable, then data will be at hand which will enable the establishment of such institutions to be made in the most efficient manner.

RADIATION TREATMENT OF LYMPHOID TISSUE OF THE UPPER RESPIRATORY TRACT

As is well known, primary infections of the lymphoid tissue in the pharynx, especially the nasal pharynx, may extend to the sinuses, ears, larynx, bronchi, and lungs. This is especially true in children, as was emphasized by Crowe.[15] Infection here results in hyperplasia and hypertrophy of lymphoid tissue. Even after adequate removal of the tonsils and adenoids, if infections continue to recur, the posterior and lateral walls of the pharynx become studded with nodules of lymphoid tissue, a condition commonly described as "granular pharyngitis." Nasopharyngoscopy will often show the same condition more frequently and in a more advanced stage in the nasopharynx. Because, in this region, lymphoid tissue is an integral part of the mucous membrane, it cannot possibly be removed entirely unless the entire thickness of mucous membrane is taken out, which of course is impossible. The recurrence, therefore, of adenoid tissue in the nasopharynx is not due to previous faulty surgery but is the normal physiological reaction. The treatment for the recurrence is not a second operation, but irradiation. For this purpose Crowe[16] advises radon, which he has been using for the past seventeen years. This is especially valuable in treating recurrences of lymphadenoid tissue which may block the internal ostia of the Eustachian tubes and thus cause impairment in hearing.

Next to the sex cells, the lymphocytes are the most sensitive cells in the body to beta and gamma irradiation. Therefore, in treating these patients, the dosage employed is so small that there is no danger of a burn or a dry nasopharynx. Under irradiation treatment, the lymphoid mass gradually shrinks and finally disappears, leaving a smooth mucus membrane not unlike that of the nasal septum. This method of treatment, Crowe points out, is of the utmost value in treating children who have recurrent upper respiratory infections which are apparently due to recurrent or persistent infection of the follicles of lymphadenoid tissue in the pharynx which have not been removed surgically and which are not amenable to surgical treatment.

More recently, instead of using radon for such treatment, the tendency has been to use the roentgen ray. Swihart[86] reports a series of ten cases in children ranging in age from four to thirteen years, in whom repeated upper respiratory infections, often accompanied by tonsillitis and occasionally hearing impairment, were treated by the roentgen therapy of hypertrophied lymphadenoid tissue in the nasal and oral pharynx with strikingly good results. Many of these children had not been helped by tonsillectomy and adenoidectomy.

ATOPIC DERMATITIS

Robinson[71] has reported on a group of children with eczema from both clinic and private practice. There were 426 cases in the clinic group. About one-quarter of these improved and remained in a satisfactory condition with only local treatment. The results of hospitalization were uniformly good. Of the nonhospitalized dispensary patients who did not readily improve under local treatment, the results were consistently poor. There were 168 private patients. In eighteen, the eruption began a few days after birth; in ten, at one month of age; in twenty, at two months; in ten, at three months; in twelve, at four months; in forty-eight, at five months to one year; in twenty-six, in one to two years; and in twenty-three, between the ages of two and six years. Of these patients, thirty-two did not improve satisfactorily on home treatment and went elsewhere. The others improved either at home or in the hospital.

Robinson employs all means of treatment: environmental control, dietary, and local. His article contains a good historical review of the subject. Environmental control is emphasized. He states that the child should be handled as little as possible, preferably only when a change of diapers is needed. If the child is held, the holder should not use nail polish, perfume, or perfumed powders, and preferably should not wear silk, wool, furs, or rayon. He finds that, in his experience, compound resorcinol ointment has occasionally succeeded when all other medication has failed. It was necessary in some instances to use mechanical restraining devices after hospitalization before improvement could be noted. In Robinson's opinion, these patients had developed a habit itch.

Another general review of the subject has been published by Brain.[5] He states that in dermatological experience infants are rarely allergic to specific foods. This is a statement which is constantly made by dermatologists. I believe it is due to the fact that dermatologists rarely see infants at the early age at which they are seen by pediatricians or pediatric allergists. By the time they get to see the dermatologist, the food elements have usually been thoroughly ruled out and there remain only the other factors. This possibly explains the difference in the point of view, although in my personal experience I see many older patients who have been studied without good results by dermatologists because the element of food allergy has been neglected.

Brain makes the interesting statement that the emotional relationship between mother and child may clearly account for exacerbations of eczema and states that some authorities believe that breast feeding should be discontinued on this account. Focal sepsis may be important, particularly in chronic eczema of the hands and feet. He states that much can be done to toughen the skin by exposure to air and sky shine. The naked skin is stimulated to exercise its powers of adaptation, and there is much evidence that insulation of the skin by overclothing perpetuates the eczematous state. On the other hand, an actinic dermatitis is just as likely to aggravate the condition considerably and, when once acquired, light sensitization may be most difficult to cure.

The Latin-American aspect of infantile eczema has been considered by Salas-Garcia.[74] The literature is reviewed at length and the views of earlier authors, chiefly concerned with etiology, are given. There is no original material and no case reports. There is a section devoted to treatment, chiefly dietetic, with mention of many patent preparations, but this also contains nothing original. It is difficult to abstract a review of this nature.

A very interesting study of infantile eczema with particular reference to inheritance and prognosis has been published by Edgren.[26] The material consists of 395 patients (240 boys and 155 girls) who were studied in Uppsala and Stockholm because of eczema during the first two years of life. The original observations were made between 1903 and 1924. The control material consisted of 465 patients (284 boys and 181 girls). None of these had eczema or any very serious illness.

Edgren observed that bottle feeding, as compared with breast feeding, did not appear to predispose to eczema. This is directly contrary to the work of Grulee and Sanford.[37] These authors studied the incidence of eczema in 20,061 infants. The results of their investigations showed that the incidence of eczema was lowest in the breast-fed infants. There was twice as much eczema in partially breast-fed infants as those completely breast-fed and seven times as much eczema in bottle-fed as in breast-fed infants.

There was no evidence in Edgren's series that low birth weight predisposed to eczema; the contrary appeared to be true. While girls appeared to develop eczema somewhat later than boys, eczema was more common in boys than in girls. The average duration of the eczema in both sexes was about one and one-half years.

Infants with mild forms of eczema are less likely to have ill health and develop other allergic manifestations than infants with severe eczema. Children whose eczema begins early are more likely to have ill health and develop subsequent allergic manifestations than children whose eczema starts later. The chances of developing chronic atopic dermatitis are greater in those infants in whom the eczema starts early than those in whom it starts late, and are also greater the more widespread the eczema. Edgren found that the frequency of allergy in the family history of children with allergic disease is greater than in the control group. It was also true that the less allergy in the parents, the less apt was the eczematous child to have ill-health and develop other allergic manifestations. Twenty-one per cent of the eczematous children continued to have some form of ill-health and 42 per cent were classified as having unstable health.

Almost 50 per cent of the eczematous children developed some other allergic disease. These, in comparison with allergic manifestations developed by the controls, are as follows:

	Eczematous Children (per cent)	*Control Children (per cent)*
Urticaria	27	6
Asthma	23	2
Hay Fever	10	2
Strophulus	5	2
Angioneurotic edema	2	1

Only 10 per cent of the control patients developed allergic disease. The danger to life of infants with eczema appeared to be no greater than when there was no eczema. No cases of so-called "eczema death" occurred in this series.

ERYTHRODERMIA DESQUAMATIVA

Glaser and Markson[36] have briefly reviewed the literature concerning erythrodermia desquamativa (Leiner's disease). Apparently it is rarely seen in this country in the typical form originally described by Leiner and, when it occurs, is differentiated with difficulty from atopic erythroderma and seborrhoeic dermatitis, exhibiting as it does many features of both diseases. From the data given, the case described is not typical of erythrodermia desquamativa. This condition was suspected because the patient, after suffering from atopic dermatitis which failed to respond to the usual methods of treatment, developed many of the symptoms of Leiner's disease with a scaling dermatitis, intermittent edema, toxemia, diarrhea and finally death. The illness began at the age of three months; a marked change for the worse occurred at the age of seven months, at which time erythrodermia desquamativa was diagnosed; and the child died at the age of ten months. The late date of the onset of the condition and the fact that it followed a typical atopic dermatitis leads the reviewer to believe that it probably was a case of atopic dermatitis of progressive severity which terminated fatally despite all therapeutic efforts. It seems unnecessary to assume that hypoproteinemia is diagnostic of Leiner's disease, since this occurs not infrequently in atopic dermatitis where drastic dietary therapy is attempted.

A case of the celiac syndrome which developed in an infant who had previously been reported[88] as suffering from Leiner's disease (erythrodermia desquamativa) is noted by Thelander.[89] The celiac syndrome started sometime after the age of eight months, after the patient had apparently completely recovered from Leiner's disease. The child appears to have made a gradual recovery which was almost complete when she was last reported upon at the age of eight years.

Simon[80] has reviewed his interesting work on the relationship between human dander and atopic dermatitis. He found that patch tests with human dander were positive in twenty-six of thirty-one children with atopic eczema. It is difficult to understand Simon's statement that conclusive evidence that foods are important allergic excitants of atopic dermatitis is lacking, in view of the everyday experience of pediatricians with atopic dermatitis unquestionably caused by foods especially milk and usually even more strikingly and unmistakably caused by egg. In my experience with infants up to three years of age suffering from atopic dermatitis, in a series of nineteen cases, positive patch tests with human dander were elicited in seven instances. However, in no instance could a causal relationship be established between human dander and the child's dermatitis. In this connection, Stroud's[83] remark, that the method which Simon advocates for keeping human dander away from an affected child may keep other probable external allergens away and thus benefit the patient indirectly, is very pertinent.

DeForest and Kerr[18] have described an interesting reversal of the usual course of events, in that an infant with infected eczema caused an epidemic of streptococcal infection in a group of nurses working on a pediatric floor rather than the infant's contracting the infection from a nurse. The patient described was a boy, two years of age, admitted with a generalized, fiery red eczema with a left purulent otitis media. Group A, type 14, hemolytic streptococcus was recovered from the skin. Later, the same organism was recovered from nose and throat cultures. During a three-month period, seventy-four nurses took care of this child, and half of them developed streptococcal infections about evenly divided between sore throats and scarlet fever. The parents and relatives who had taken care of the child previous to admission had also developed various infections, presumably of streptococcic origin. This case illustrates the high degree of communicability which hemolytic streptococcal infection in infancy may acquire.

Sulzberger and Baer,[85] commenting upon the above report, state that in their not inconsiderable experience with severe, continually scratched and traumatized atopic dermatitis, they have not seen a single instance of severe invasive infection with staphylococci or streptococci. Four cases of erysipelas complicating atopic dermatitis in infancy were reported by Glaser and Edwards,[35] but the comment of Sulzberger and Baer is essentially correct. While eczematous children not infrequently develop complications caused by cocci, they are nearly always infections of the respiratory or gastrointestinal tract, and the portal of entry does not appear to be the skin. The probable explanation is that the same reactive properties of the skin which result in atopic dermatitis also enable the skin to react effectively against the common skin organisms.

As an illustration of how much in the way of infection a child with allergy may occasionally tolerate, Fischer and McClure[29] report the case of a five-month-old male Negro infant in whom nutrition was a problem because of severe food allergy, manifested in part by eczema, which made intravenous injections difficult or impossible. The child was originally admitted because of eczema, bronchitis, and septic type of temperature elevation. He was hospitalized for 127 days, and during this time he also had clinical evidence of persistent upper respiratory infection, bronchitis, thrush, three episodes of diarrhea, furunculosis of the scalp and forehead, cervical lymphadenopathy, and multiple subcutaneous abscesses. A septic type of temperature curve persisted. The positive laboratory findings were leukocytosis, positive

cultures for staphylococcus aureus hemolyticus of the scalp furuncles and the subcutaneous abscesses, a predominence of staphylococcus aureus in the throat culture, and one positive blood culture for staphylococcus anhemolyticus. The child responded well to penicillin, which was probably also responsible for other negative blood cultures. Where parenteral amino acids were given, subcutaneous abscesses developed. The authors believe that this was due to secondary infection from the blood stream.

DIETARY TREATMENT OF ATOPIC DERMATITIS

The use of strained meats, first described by Rowe,[73] and used by Glaser,[32] as a protein basis for milk substitutes in the treatment of milk allergy, has been discussed in the first of these reviews.[33] Since the preparation described was made by a commercial house and was not generally available, Stuart[84] evolved a method by means of which these meats may be prepared in any hospital diet kitchen or even at home. This is done by using one of the small commercial electrically powered homogenizers now on the market. Detailed directions are given.

In the past few months, however, there has appeared another commercial preparation of various finely liquified canned meats. The meat particles in these preparations are even more finely subdivided than those described above and are made by a different process, the nature of which the manufacturers do not care to divulge†. Because of their availability and very fine texture, these preparations should be highly satisfactory as the protein basis for artificial milk substitutes in the treatment of the milk allergy, and I have used them successfully for that purpose.

Fundamental studies in the blood chemistry of eczematous infants with special reference to lipoid metabolism have been continued by Hansen.[39] He states that fatty acids containing two or more double bonds are not synthesized by the body, and certain ones, linoleic acid (C 18 with two double bonds), and arachidonic acid (C 20 with four double bonds), are known in nutrition as the essential fatty acids. In about four-fifths of eczematous infants under two years of age and a little over one-half of adult patients with eczema, the serum iodine numbers were found to be below the normal range.

Hansen, Weise, and Miller[38] were able to raise the iodine number of fatty acids in the serum of dogs by the feeding of lard. This same procedure has been effectively applied to infants with eczema. The lard is spread on crackers or mixed with other foods and appears to be taken well by the patient. It is given in teaspoon or tablespoon quantities once or several times a day as tolerated. A therapeutic trial should comprise a period of about two months or so using 1 to 2 ounces a day.

Obviously, basic work of this nature in eczema is much to be encouraged. However, the difficulties of obtaining satisfactory controls in a disease which is usually self-limited and which at the same time may require other measures than dietary for its amelioration are self evident.

The sedimentation rate, using the Landau-Adams micro method, in fifty-four infants and children suffering from various types of eczema has been studied by Strickler and Ginsberg.[81] The normal rate as established by controls on fifteen children with tinea capitis was between 4 and 9 with an average of 6 with no variation for the male or female group. In the children with eczema, the limits were between 4 and 19 with an average between 8 and 9. The cases were divided into a low group with a rate below 6 and a high group with a rate over 6. The significance of this could not be determined. The sedimentation rate was of no diagnositic or etiologic significance; however, it did reflect to a marked degree the status of the skin provided the child was otherwise normal. An increase in sedimentation rate may be regarded as significant of probable impending complications or an intensification of the inflammatory process. A lowered rate is a fairly good

† Personal communication from Swift and Co., Nutrition Division.

index of the recovery of the skin, particularly if such a lowered rate persists over a period of time.

An article by Ratner[69] on the subject of infantile eczema, written in popular style for the layman, presents the subject in an interesting and instructive manner. It is recommended reading for the parents of a child with this disease.

KAPOSI'S VARICELLIFORM ERUPTION

This disease, which was discussed in considerable detail in the second of these reviews,[34] continues to excite interest. Blattner, Heys, and Harrison[3] describe a case of Kaposi's varicelliform eruption in a fifteen-month-old infant with atopic dermatitis. The patient made a good recovery, and herpes virus was isolated from the lesion. Jaquette, Convey and Pillsbury[45] have reported another case with recover in a six-month-old Negro infant with eczema. The studies suggested that herpes virus, possibly in association with staphylococci and streptococci, was involved in an etiologic relationship in this case.

CONTACT DERMATITIS

Dobes[22] has described five cases of diaper rash in infants ranging in age from two to sixteen months. The rash appeared as an acute erythema accompanied by a mild edema. Pruritus was present in all cases and vesiculation in one case. Careful studies showed that the rash was due to a preparation called Perm-Aseptic-Ramplex. The purpose of this preparation is to make textiles actively antiseptic, to protect persons as well as to prevent the destruction of textiles by micro-organisms. It is widely used among diaper services in dilutions of 1:10,000 to 1:30,000. Each case cleared in from three to seven days. The patients had worn the treated diapers for at least two months before sensitization occurred.

Pedrera[61] reports the case of a baby five months old who immediately developed a severe dermatitis with edema following the application of highly diluted alibour water to the face and scalp. A patch test on the arm was positive for this preparation which contains sulphur, copper, and zinc. There was no family or personal history of allergy. He also reported the case of a girl twelve years old who was given a drop of argyrol into each eye because of conjunctivitis. There was immediate itching and lacrimation with swelling extending over the lower lids to the cheek. There was no accompanying fever and the patient recovered in three days. The child had previously had some urticaria but there was no family history of allergy.

URTICARIA

Bivings[2] has discussed in detail a condition which is much commoner in pediatric practice than is generally realized. This is what he terms "acute infectious urticaria." The scant literature on this subject is reviewed and the author reports twenty-two consecutive cases of acute urticaria in children associated with acute infection. The history was negative for allergy in eighteen cases, positive in three, and unknown in one.

The syndrome is characterized by urticaria, usually with angioneurotic edema, fever, and a demonstrable focus of infection. In this series, the throat was most commonly the focus, with otitis media and pyelitis accounting for the remainder. The urticaria could not be explained on the basis of drug sensitivity or the ordinary allergic types of sensitivity except in one case. Four typical cases, ranging in age from ten months to seven years, were reported. The limited bacteriological study showed no common organisms. The youngest patient was described as having a fever of 37.8° C. (100° F.) rectally. While it must be admitted that the standard for a normal rectal temperature in infants and children has never been officially established, it is the reviewer's practice to regard no rectal temperature as evidence of fever unless it is over 37.8° C. (100° F.). Even higher temperatures, at least

up to 38.7° C. (101° F.) may occur in the absence if the temperature happens to be taken after exercise.[7,41] It must be remembered in this connection that crying is a form of exercise in this age group.

It is well known that urticarial eruptions resembling the papular urticaria of older children occur in the newborn. Indeed, urticaria may be regarded as the first clinical manifestation of allergy to occur in the human being. Ström[82] made an interesting study of this condition by feeding fifty-eight recently delivered mothers three oranges a day during their stay in the hospital. Urticaria appeared in twelve (22 per cent) of the nursing infants of the test group and in only two (3 per cent) of the control group. Urticaria could not be produced by feeding the mothers 100 mg. each of ascorbic acid daily, so presumably the rash was not due to vitamin C. There were two cases of very extensive urticaria in the infants of the orange-fed mothers. The rash disappeared soon after withdrawing the oranges from the diet. In one of these, the urticaria recurred when the mother was fed orange again. In the course of the study, a case similar to this latter was observed due to chocolate ingested by the mother. The author further states that drugs administered to the mother must also be considered as a possible cause of urticaria in the nursing infant.

Eder,[25] in discussing the prophylaxis and treatment of allergic disease in early infancy, advises elimination from the diet of the nursing mother of what he has found to be the five most common offenders: cream, oatmeal, egg, chocolate and nuts (including peanut butter). The only one of these in reviewer's experience which has ever caused trouble has been egg. Chocolate does cause trouble, as mentioned in the preceding paragraph, and the first clinical report on this subject of which I am aware was that of Talbot[87] who reported that eczema could be cured or produced in the case of one individual baby by withdrawing or including chocolate in the mother's diet. The peanut is regarded as a nut by most laymen and many physicians. It is, however, not a nut but a legume (pea and bean family) and since legumes tend to react as a group, if one causes trouble it is best to avoid all until the guilt or innocence of each is proven.

The use of benzedrine sulphate for the treatment of urticaria in children has been advocated by Roberts.[70] In the cases of ten children with urticaria varying in age from two and one-half to six years, benzedrine sulphate was used in starting doses of 2.5 milligrams every three to four hours. All children were relieved except one child, three and one-half years of age, who had developed urticaria seven days after receiving tetanus antitoxin. Two children, aged four and nine years, respectively, required 5 milligram doses every four hours for relief. One child six years of age with chronic urticaria was relieved twice by benzedrine sulphate and then disappeared from observation. Disagreeable side reactions from the use of this drug, particularly wakefulness, excitement, and loss of appetite, were not mentioned. The author recommends that fluids and laxatives also be employed properly in this condition. This report is of considerable interest, particularly with regard to the reaction of children to benzedrine. However, the reviewer believes, because of personal experience with these preparations, that benadryl and pyribenzamine will be the drugs of choice in the treatment of urticaria and angioneurotic edema in this age group as well as in older children and adults.

POLLINOSIS

A case of hay fever occurring in New Jersey in a four-month-old boy was reported by London.[54] The symptoms were characteristic for the disease. The scratch tests showed positive reactions to short and giant ragweed and cocklebur. Treatment by the injection or ragweed extract was started and symptoms were greatly alleviated within a few days. This case was first treated in August of 1942.

There was no recurrence of the hay fever in subsequent seasons. This is interesting since he received no treatment after the first season. The author states that this case suggests the possibility that early institution of hay fever treatment during the first season of its occurrence may result in a rapid cure. The age at which hay fever may start doubtless depends upon the susceptibility of the individual and the amount of pollen present in any given locality. Kahn[46] states that in certain parts of Texas newborn infants may develop symptoms of pollinosis shortly after birth. The youngest patient I have seen with hay fever was an infant six months of age. The symptoms were mild the first year, and treatment was not instituted until they again recurred when the child was eighteen months of age. She has required continuous treatment since then, and the child is now sixteen years of age.

OTITIS

Hiller[42] has reviewed the subject of allergic otitis media with particular reference to the work of Hansel, Proetz and other Americans. The author reports the case of a fourteen-year-old girl with a history of allergy (perennial allergic rhinitis and urticaria) who gave a marked reaction to a staphylococcus vaccine. She had four attacks of otitis media, one of which was followed by mastoiditis. Angioneurotic edema of the face and allergic rhinitis had always preceded and accompanied the attacks of otitis. The condition was kept under control by vaccine, and there was no further recurrence of the otitis.

PURPURA OF ALLERGIC ORIGIN

An interesting case of Henoch-Schönlein purpura and acute nephritis due to food allergy is reported by Brown.[8] A nine-year-old boy had been hospitalized three months before the present reported admission because of colicky abdominal pain, vomiting, bloody stools, a stiff left hip joint, and a purpuric rash on the trunk. Because of rigidity and tenderness in the right iliac fossa, it was felt necessary to do an appendectomy. This revealed a kinked but otherwise normal appendix, which was removed without relief of the patient's symptoms. Over a period of one month after operation the symptoms gradually subsided and the patient was discharged. He was again readmitted to the hospital three months later because of blood in his stools of two weeks' duration. His urine was normal at that time. After a week's observation, he was discharged with a diagnosis of allergic purpura. The week following, he had two attacks similar to those for which he had been hospitalized three months previously, also accompanied by urticaria and hematuria.

It was observed that both of these attacks occurred on Sunday and each attack occurred two hours after the evening meal containing various foods including tomatoes. By elimination diets, it was found that the symptoms could be reproduced by feeding tomatoes, and on two occasions the boy gave positive scratch tests to the pulp but not to the skin of tomatoes. Tomatoes were omitted from his diet, but three months after the last attack, the urine contained red and white blood cells and granular casts, though there had been no symptoms during that time.

The literature of this subject is reviewed, and the author states that he saw a patient who came to autopsy with chronic nephritis eleven years after an atypical attack of allergic purpura associated with hematuria. When bacterial allergy is the apparent cause, the probability of recurrent attacks and repeated damage is considerable. Where food allergy is responsible and the offending food is avoided, the prognosis may be less serious.

Njå[59] has reported a case in a year-old child of what is probably another variety of allergic purpura, occurring in a younger age group and first described by

Seidlmayer[77] in 1939 under the name of "Die frühinfantile, postinfektiöse Kokarden-Purpura." This disease occurs in infancy and childhood up to the age of three years and is commonly associated with upper respiratory infection. Characteristic purpuric eruptions appear, which may be as large as the infant's hand in some cases. These usually occur in the center of urticarial or edematous areas and are localized chiefly to the extensor surfaces of the extremities, the buttocks and face. Hematuria is uncommon but occurred in Njå's case. In this case also, skin tests with bacteria were negative except to pneumococci, which gave large hemorrhagic reactions. This suggests allergy to infection. The prothrombin time in this case was greatly prolonged (in excess of five minutes) and this became normal when the hemorrhage ceased. The disease is closely related to Hennoch-Schönlein's purpura and differs from this mainly through its occurrence under six years of age and the absence of joint and abdominal symptoms. It might be regarded as another variety of this disease in a younger age group.

PERIARTERITIS NODOSA

Two cases of periarteritis nodosa occurring during the first month of life and discovered at autopsy are reported by Wilmer.[94] This brings to four the number of reported cases of this disease occurring during the first year of life. Both of Wilmer's cases occurred in colored children. In both, there was leukocytosis but no eosinophilia, and typical foci of periarteritis nodosa were found in various organs. The first patient was a girl who developed symptoms at the age of twenty-five days and died twelve days later, at which time the probable clinical diagnosis was septicemia or renal thrombosis. The only family history of allergy was in the case of the mother who had hives from tomatoes. At autopsy, there was a large inflammatory-necrotic mass involving the right adrenal, containing large numbers of unidentified cocci. The second case was a boy who died at the age of ten days after an illness of two days. Pus could be expressed from his umbilicus and it was believed that he had a septicemia. The family history for allergy was not obtainable.

DRUG ALLERGY

The incidence of reactions to sulfonamide drugs in an estimated 5,000 infants and children is reported by Fink and Smith.[28] Most of the patients received sulfadiazene, some sulfathiazole and some sulfamerazine. Sixty patients (1.4 per cent) developed febrile reactions, twenty-five with accompanying rashes. There were only eight additional important complications: two cases of malignant neutropenia, two cases of hemolytic anemia, and four cases of anuria. All recovered except two cases of anuria, both of which had received sulfathiazole. Over half (59 per cent) who proved sensitive to one course of sulfanilamide developed immediate reactions to tests with repeat doses. Test doses of 0.25 gm. (grains 3.8) were usually sufficient to produce a reaction. Immediate reactions were observed only in those patients who had shown previous drug reactions. Seven children were given test doses of a sulfonamide different from that to which they were proved sensitive. Only two developed reactions and both of these received a third sulfonamide without trouble. Skin-testing of suspected sulfonamide sensitive patients with human sulfonamide-containing serum, after the manner of Leftwich,[51] was not found useful by the authors. Renal complications were rare, and the authors feel that it is unnecessary to supplement sulfonamide therapy with alkali. They conclude that untoward reactions to sulfonamides are infrequent in infants and children and rarely cause serious effects.

Pedrera[61] has reported six interesting cases of drug allergy in children. Two of these were due to acetylsalicylic acid. One occurred in a boy twelve years of age who had never before taken any preparation containing this drug. Follow-

ing the taking of a popular headache remedy, there was a sudden edema of the eyelids and loss of voice due to edema of the larynx. This was followed by dyspnea, dysphasia, and intense headache. Complete relief was very rapidly obtained from the injection of epinephrine. The patient was known to be allergic to chocolate. He had had asthma as an infant and also had a mild perennial allergic rhinitis. There was no family history of allergy. Whenever he ingested acetylsalicylic acid, he would develop atopic dermatitis and occasionally bronchitis and coryza with edema of the lids.

Three cases of allergy to sulfonamides are described. One occurred in a girl twenty-two months of age who was given sulfanilamide because of a sore throat. On the second day after starting the medication, each dose was followed by vomiting, pallor, cyanosis, and alarming peripheral circulatory failure. Recovery was complete within two days after stopping the drug. The child had never before taken any sulfonamide drugs. The second case was a boy fifteen months of age who was given sulfathiazole because of tonsillitis. On the third day there was a generalized maculopapular eruption and swelling of the lids. This was unaccompanied by fever. The rash disappeared on the fourth day. There was no history of previous sulfonamide treatment and no family or personal history of allergy. The third patient was a girl seven years of age who received sulfonamides on several previous occasions for tonsillitis. The family and past personal history as far as allergy is concerned was not mentioned. About two weeks after the last attack of tonsillitis, oral sulfathiazole was administered because of fever and cervical lymphadenitis. Three days later an eruption appeared which quickly spread over her entire body. This was at first bright red but changed rapidly in appearance and disappeared on the fourth day. The rash was accompanied by high fever the first two days.

Two other cases were due to sensitivity to mercury. One was a girl eight years of age who would develop dyspnea caused by merthiolate in nasal drops. She had previously had a contact dermatitis caused by a green dye in a dress. This dye was not identified but patch tests to the green cloth were positive. Her history revealed mercurial ointment used for suspected syphilis had previously provoked such an intense dermatitis that it had to be discontinued. There was no family history of allergy.

Another patient, a girl seven years of age, had what was probably cyclic vomiting. Usually, intramuscular injection of luminal had given good sedative results, but on her last attack this reacted in the opposite manner, causing great excitement. Cutaneous tests were positive for several foods and the child seemed to improve after these were excluded from her diet.

A boy eight years old had a fixed eruption, more pigmented than inflammatory, on the anterior portion of both legs. This was shown to be due to phenolphthalein which had been used as a coloring matter in tooth paste.

Pedrera believes that drug allergy is the most appropriate term to describe the majority of abnormal reactions to medicinal drugs.

In another publication, Pedrera[63] stresses the dangers of the therapeutic and prophylactic injections of horse serum in children. He advises the use of serum derived from other animals when possible but does not consider this very practical. It is unfortunate in this connection that the manufacture of bovine tetanus antitoxin[31] in this country has been discontinued. The use of toxoid for prophylaxis is stressed. This article is largely derivative and there are no original case reports.

PSYCHOSOMATIC ASPECTS OF ALLERGY

Bowen[4] expresses the opinion that while allergic children as a group present some interesting extremes as regards mentality, if taken as a class they show no more variation in mental ability than the average. It should be emphasized with

these children that they are expected to follow the same principles of social responsibility for the rights and privileges of others as the nonallergic group.

The hyperkinetic child is the patient described by Schneider[76] who is commonly recognized as the "nervous child," or the "fidgety child," or the child who "never sits still." Among the physical abnormalities contributing to hyperkinetic behavior, the author discusses the role of allergy, and states that possibly too little attention is given by the general physician and pediatrician to the role of allergy in either causing or accentuating emotional disturbances. He quotes Karnosh[47] as stating, "It becomes more and more evident that this reaction (i.e., allergy) involves every level of the nervous system from the highest and most elaborate centers of the cortex to the humblest sympathetic terminal in the capillary loop of the skin." The author also reviews the work of Clarke[13] with reference to allergy as a cause of cyclic vomiting, infantile convulsions, temper tantrums, petit and grand mal, abdominal pain, inattention, unruliness, surliness, disobedience, and incorrigibility.

Schneider describes the case of a hyperkinetic ten-year-old child who started out life with pylorospasm followed by many food allergies and later insomnia. Her activity was so excessive, at times amounting to wildness, that she was placed in nursery school at the age of two and one-half years. By the time she was eight and one-half years of age, her hyperkinetic drive was so disrupting to the family that she was placed in boarding school. Recurrences of attacks of uncontrolled behavior led to hospitalization at the age of nine and one-quarter years. Here she gave numerous positive skin tests, and therapy from the allergic standpoint was followed by marked amelioration of the child's behavior problems within a three-month period.

Dees[17] states that in the complex problem presented by the allergic child, psychiatric factors often play a major role and are more often closely related to the production of illness than any other single nonallergic factor. Several very interesting case histories are reported. One was a twelve-year-old dust sensitive asthmatic boy who did very well for a year on the usual measures employed for the treatment of this condition. The asthma recurred when his father entered a hazardous branch of the military service. It was discovered that the boy had a marked feeling of insecurity without his father and this feeling was unconsciously made even worse by his mother's attitude towards the problem. The asthma promptly stopped when the door of the boy's dust-free bedroom was left open at night so that he felt less isolated.

Another case was a boy seven years of age whose parents were separated. The boy had asthma every time he was taken to stay with his father in town. He was clinically sensitive to pollens and farm animals but remained relatively well while living with his mother on a farm. He had asthmatic attacks whenever his parents quarreled.

These two cases represent one of the commonest forms of maladjustment seen in asthmatic children. This results from a fundamental feeling of insecurity due to over-attachment to one of the parents. This is secondary to the overprotection which the child suffers as a result of the allergy.

The allergic child who uses his affliction to obtain fulfillment of his wishes or to avoid anything disagreeable is well known. Dees describes the case of a nine-year-old asthmatic girl who, although completely asymptomatic, could bring on an attack of asthma at will when confronted with something unpleasant, such as impending skin testing. In this particular case, allergic measures were successful with the exception of occasional attacks of asthma when her desires were thwarted.

Abnormal behavior may occur as a chronic condition in practically all allergic diseases. The most common complaints are over activity, hyperirritability, sleeplessness, unreasonableness, thumb sucking, enuresis, and temper tantrums. Exacer-

bation of these symptoms may precede an exacerbation of the allergic condition. One of the earliest signs of improvement in the underlying allergic condition may be evidenced by parallel improvement in disposition and behavior.

Dees states that investigations now in progress seem to indicate that a large number of children with asthma and eczema have abnormal electroencephalograms which tend to become normal with control and improvement of the allergy. She reports one ten-year-old child with a slightly abnormal electroencephalogram who suffered from head bumping. This appeared to be very definitely related to his allergy. These observations recall the work of Shulman[78] on the use of dilantin sodium in bronchial asthma. The reviewer gave this a fairly extensive trial in an unselected number of cases (asthmatic children whose electroencephalograms had not been studied because facilities were not then available) without beneficial results.

Dees states that she has been unable to find children with eczema or urticaria on a purely psychogenic basis such as is seen in adults. She notes that there does appear to be an occasional epileptic child who is relieved by allergic management without other drug therapy.

Arena,[1] in discussing the above presentation, expressed the point of view which is probably favored by most pediatric allergists, namely that many of these behavior problems are secondary and not primary. By this is meant that they are secondary to the stress and strain brought on by the allergic attacks. If the child did not have these attacks, the chances of his developing a behavior problem would be greatly diminished. Arena also makes the statement that, during an asthmatic attack, the parents and others at home with the child are very often in a state of fright and disorganization. Besides specific therapy for relief of the asthmatic attack, the child needs to be in a calm, quiet, reassuring atmosphere. This point has also been stressed by Bowen.[4] Continuing the discussion on these presentations, Lowenbach[5] states that one should not too readily seek the assistance of a psychiatrist in children with allergy but that every effort should be made to solve the problem from the allergic standpoint. If this does not appear to be progressing satisfactorily, then the parents may be gradually prepared for cooperation with a psychiatrist.

DRUGS

Logan[53] has briefly reported on the use of benadryl in the treatment of eighteen children suffering from various allergic diseases. Both the elixir, which contains 10 mg. of benadryl per 4 c.c. (teaspoon), and the capsule, which contains 50 mg., were used. Where a fraction of a capsule was used, the powder was removed and administered in syrup or jelly. In the whole group of eighteen children, only two untoward reactions, drowsiness and vomiting, occurred. The suggested dose of benadryl is 2 mg. per pound of body weight per twenty-four hours, divided into from two to four doses. The frequency of administration should depend upon the duration of the effect, which may last from two to twelve hours. The effect should be noted within thirty or forty minutes as a maximum. Twelve of the patients had seasonal hay fever and were treated only during the season. Three of the patients had asthma. The results of the treatment of the hay fever were recorded as excellent or good in nine cases, fair in one, questionable in one, and no effect in one. The results on associated asthma which occurred in three cases were recorded as good in one case, fair in one, and questionable in another. One two-year-old child with urticaria was completely relieved. Of two children with vasomotor rhinitis, one received excellent relief and the other apparently very good relief.

One patient three years old with nephrosis would have an urticarial reaction following every infusion of plasma. The administration of benadryl before and after this procedure gave great relief to this condition. One case of angioneurotic

edema and urticaria following tetanus-gas gangrene antitoxin received complete relief from benadryl.

The reviewer is of the belief that benadryl and pyribenzamine are of considerable help to the pediatrician. The full extent to which these drugs may be used with reference to the conditions in which they might be indicated has not yet been explored. Both benadryl and pyribenzamine have been used extensively in my practice and, as nearly as I can tell, their effect and side reactions are practically identical. Occasionally, one of these drugs will be of assistance where the other one will not. Also occasionally, one of the drugs will cause disagreeable side reactions and the other will not. It is fortunate to have two such drugs so that one may be tried when the other one will not help or does not agree. In general, these drugs give remarkable relief in urticaria; they are of great assistance in the sneezing and running nose of hay fever; they are of a fair amount of help in perennial allergic rhinitis; their use in bronchial asthma is disappointing. Occasionally, a patient appears to get very definite relief. I have the impression that this occurs especially when the asthma is due to food allergy. They give no relief in intrinsic asthma. These drugs are also of considerable value in relieving the pruritis of atopic dermatitis and also are worth trying in pruritis of any other origin which has not responded to the usual measures of treatment. However, here the effects are variable and inconstant.

In the first of these reviews[33] it was stated that privine for use in nose drops was supplied in two strengths, 0.1 per cent and 0.05 per cent. It was further stated that these two strengths were used because at times the drops appeared to cause sedation. This cannot happen very often because but one report of this condition, that of Waring,[92] has appeared since privine was introduced several years ago. He reports the cases of two girls, ages three months and seven years respectively, who, following the administration of privine hydrochloride 0.05 and 0.1 per cent respectively in the appropriate doses, developed marked somnolence. Another boy, three years of age, drank an unknown amount, probably 7 or 8 c.c., of privine hydrochloric 0.05 per cent. He soon became quite drowsy and remained so for several hours afterwards.

Boric acid ointment is a preparation which is very commonly used in the treatment of infantile eczema. While it is well known that boric acid solution by mouth may be highly toxic to infants and young children, it is not generally realized that rarely it may also be toxic as an ointment. Watson[93] has briefly reviewed the literature on boric acid poisoning. He states that boric acid is a drug which is almost entirely ineffective and may be dangerous, even when used in ordinary ways. He reports the case of a four and one-half-month-old boy with severe generalized weeping infantile eczema, treated first with boric acid soaks for two days and then with boric acid ointment for two days. The infant developed fever, convulsions, and an intense generalized erythema. The convulsions gradually ceased, but the child became deaf and then comatose and died three weeks after the onset of the convulsions.

Repeated spinal fluid examinations were negative for evidence of infection until a few days before death, when the child developed a terminal pneumonia and pneumonococcus meningitis. Tests for boric acid in the spinal fluid and urine were strongly positive during the first week. The diagnosis of boric acid poisoning was suggested by the similarity in behavior of this child to infants accidentally poisoned by boric acid. The intense erythema, giving the child the appearance of a boiled lobster, is an outstanding characteristic.

Boric acid ointment is further discussed by Pfeiffer, Hallman and Gersh.[64] They state that boric acid, whether applied in the form of an ointment or a saturated solution to extensive wounds, is a cumulative poison. The weak antiseptic value of boric acid suggests that, for medicinal use, other more active and less po-

tentially harmful therapeutic agents should be employed. The best antidotes for boric acid poisoning are the intravenous administration of plasma and large intravenous injections of isotonic solution of chlorides.

HAPAMINE

Anyone who attended the annual meeting of American Academy of Allergy in December, 1945, would have been convinced that as a therapeutic agent hapamine was without value except perhaps as a nonspecific therapeutic measure whose use was not without danger. Eder[25] has since reported the use of this preparation in seventeen cases of allergic rhinitis in children, fourteen of whom were under the age of five years. Seven cases had asthma and three had atopic dermatitis. It is stated that the results have been almost too good to be believed and all the allergic manifestations in these patients were apparently benefited by the hapamine. Three illustrative case reports are given. In the first case, the hapamine treatment was started in September, 1945, and the child showed improvement from the first dose; in the second case, treatment was started in October, 1945; in the third case, the history does not mention that the child had allergic rhinitis but she did have recurrent upper respiratory infections and asthma. All these children were apparently completely relieved. Treatments were started in December, 1945. Since the article was published in May, 1946, it must have been submitted for publication at least a month earlier. Therefore, even if one grants immediate improvement from the time of starting of the hapamine therapy, the longest interval of relief was five months. It is my experience that one cannot be sure that any single measure has produced complete relief of allergic rhinitis unless the duration of relief is at least one year. In this part of the country (New York State) many children with perennial allergic rhinitis suffer exacerbations during the summer because of pollen. This is especially true in the last part of August and September when the ragweed pollen is especially plentiful. Any therapeutic measures administered at this time will often appear to give relief because from then on the atmospheric pollen gradually diminishes. For this reason, I do not consider any patient to have obtained satisfactory relief from any therapeutic agent administered unless he has been free from symptoms for at least one year or a complete pollen cycle. While pollen conditions are doubtless different in Santa Barbara, California, than in Rochester, New York, the same principle doubtless obtains. A report from Eder after a few years on the condition of these patients would be a useful contribution to our knowledge of hapamine. My personal experiences with this drug have been both disagreeable and unsatisfactory.

MISCELLANEOUS

A detailed study of 289 cases of allergy in children has been reported by Torroella.[90] The children were classified according to their major allergic disease as follows:

	Cases
Asthma	124
Urticaria	81
Chronic Atopic Dermatitis (Hebra's prurigo)	26
Allergic Rhinitis (vasomotor rhinitis)	21
Atopic Dermatitis	17
Infantile Eczema	16
Allergic Purpura	1
Migraine	1
Gastro-intestinal Allergy	1
Contact Dermatitis	1

Under each subdivision of the above, the author gives the results of skin tests, therapy, and his result. In his practice, allergic children make up 17.1 per cent

of the total number of allergic patients. More patients (42.6 per cent) belong to the second period of childhood than to the first or third period. Asthma is the most frequent manifestation (42.9 per cent) and urticaria the next (28 per cent). The various skin allergies make up 48.2 per cent of the total.

Family histories of allergy may be established in 76.4 per cent of the cases. Hereditary transmission is mostly through the mother. The average age at which symptoms begin is 4.4 years. The proportion of male to female is 1:1.3. More than one allergic manifestation in the same patient was noted in ninety-four cases (32.5 per cent). For the entire group, clinical cure was reported in 32.7 per cent of cases; great improvement in 29.8 per cent; improvement in 33.9 per cent; and no improvement at all in 3.4 per cent of the cases.

While no one believes that the continuous administration of a sulfonamide compound to prevent upper respiratory infection is an ideal procedure, yet in the desperate attempt of the pediatric allergist to relieve those children who develop asthmatic attacks regularly following such infections, it has been felt that the risk of this procedure is well justified. The value of so doing, however, is still open to question. In this connection, the report of Siegel[79] on the incidence and severity of acute infections of the upper respiratory tract in 128 physically normal children, half of whom were treated by the continuous oral administration of sulfadiazine and half of whom were untreated, is of considerable interest. The drug was used between August, 1942, and April, 1944, for periods of four to fifteen consecutive weeks in doses ranging from 0.5 to 2 grams daily. The average level of free sulfadiazine in the blood was 3.5 mg. per cent with a maintenance dose of 1 gram per day and 7.2 mg. per cent with 2 grams per day. In no case was it necessary to discontinue the use of the drug because of serious toxic reactions.

The incidence of acute infections of the respiratory tract was almost the same for treated and for controlled children. However, the treated persons as a group recovered somewhat more promptly than the controls and experienced fewer complicated illnesses and fluctuations in severity. Since the illnesses observed were unexpectedly few and were milder than anticipated, the antibiotic effects of sulfadiazine were not readily demonstrable.

Kendrick, Thompson and Eldering[48] have contributed to the study of the puzzling lack of immunity to pertussis in the newborn, without, however, solving this problem. A group of pregnant women was treated with pertussis vaccine (it is not stated that Phase 1 was employed) and another group used as a control. The opsonic reactions in the treated group were twice as strong as in the untreated group and in the babies of the treated mothers were about 2.9 times that of the control group. In the treated group the babies had two-thirds of the opsonic activity of their mothers. Perhaps the lack of immunity to whooping cough in the newborn may be explained upon a quantitative basis; that is, the level of immunity in mothers is generally too low for effective protection of their offspring. Conclusions on this basis cannot be made, since it is not known what correlation there is between opsonins and protection. The results indicate that placental transfer of circulating pertussis antibodies does occur and that the higher the level in the mother the more nearly does the titer of her baby approach her own. The study indicates that under certain conditions it may be practical to treat the pregnant mother with pertussis vaccine in order to raise the level of immunity in her baby.

It seemed generally agreed, according to Rollof,[72] that erythema nodosum is an allergic skin reaction induced by different infections in individuals who have a predisposition for this disease. In tuberculosis, erythema nodosum usually appears at that stage of the process where the tuberculin reaction is changing from negative to positive. The author studied thirty-three children with primary pul-

monary tuberculosis. Erythema nodosum was provoked in twelve cases by the administration of sulfathiazole. It occurred in all cases where the patients were still in the initial fever stage of the tuberculous process. Rollof states that practically all cases of erythema nodosum occurring in children with acute infections, treated with sulfathiazole occur in association with recent tuberculous infections.

It is suggested by Epstein and Custer[27] that two peculiarities of acute lymphatic leukemia in childhood point to sensitization phenomena. These are the frequent association of its onset with infection, and the recurrence of remissions with apparent complete clinical recovery. They report a case of aleukemic lymphatic leukemia in a twenty-month-old girl who presented clinical evidence of sulfonamide sensitivity. Their studies raised the suspicion that hypersensitivity may play a role in the mechanism of leukemia, at least in that form in which it presents itself in early childhood.

Hatoff[40] treated 129 susceptible infants and children of an average age of four years by injection of an extract of the whole fleas of dog, cat and man. Each of these children had suffered unabatedly from flea bites for a period of from one week to one year. Of the treated cases, 78 per cent were benefited, 5 per cent received equivocal relief, and 17 per cent failed to respond. The work of Eder[24] in connection with flea bites is also interesting. He reports marked success in the prevention and treatment of flea bites by the oral administration of thiamin chloride. The thiamin is given three times a day for three days. In the case of infants, the dose is 10 mg.; runabout children, 20 mg.; older children, 30 mg.; and adults, 40 mg. This is followed by a smaller daily dose for several weeks.

Attention is called to the publication of a new journal, *The Quarterly Review of Pediatrics*.† This contains abstracts and book reviews of all subdivisions of pediatric literature. These are classified alphabetically under thirty-four headings, the first of which is "Allergy." In a work of this scope, the number of abstracts of articles in the field of allergy is naturally limited, but they are exceedingly well done, timely, and will be of great help to the pediatrician.

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(Continued on Page 92)

News Items

SPECIAL SESSION ON ALLERGY OF THE AMERICAN MEDICAL ASSOCIATION

On Thursday, July 4, 1946, a committee representing the American Academy of Allergy and the American College of Allergists, appeared before the Reference Committee on Sections and Section Work of the American Medical Association.

A report of the Reference Committee on Sections and Section Work (J.A.M.A., July 20, page 1000) concludes, "After consideration of the information as presented by the reports of the Academy and the American College of Allergists, the Reference Committee recommends that the question be referred to the Council on Scientific Assembly for study and recommendation."

The latter Council has arranged for a special session on Allergy to be held at the Centennial Meeting of the American Medical Association at Atlantic City on Friday, June 13, from 2 to 5 p.m. This special session will serve as a guide when establishing a Section on Immunology and Allergy. Dr. Harry Huber has been appointed chairman of the special session and Dr. Richard Kern, secretary.

Although this special session is to be held on the last day of the American Medical Association meeting, five days following the closing of the session of the American College of Allergists at the Hotel Senator, June 6, 7, and 8, every member of the College is urged to attend this meeting and help make the program a success. The program will undoubtedly be arranged to arouse the interest of the general practitioner in allergy and in no way will it conflict with the scientific session to be held by the College. If the Council on Scientific Assembly of the American Medical Association establishes a Section on Allergy or a Section on Immunology and Allergy, it means the recognition of allergy as a specialty.

This session will be observed very closely, and its future success will eventually depend upon the co-operation of the two national allergy societies by having equal representation.

* * *

SOUTHWEST ALLERGY FORUM

March 31 and April 1, 1947

WASHINGTON-YOUREE HOTEL
Shreveport, Louisiana

SUNDAY, MARCH 30, 1947

8:00 P.M.—Cocktail Party
At the home of Dr. H. Whitney Boggs, 140 Albany Street

MONDAY, MARCH 31, 1947

Morning Session—9:00 a.m.

Some Faults in the Allergist's Routine
Dr. George L. Waldbott, Detroit, Michigan
Discussion opened by Dr. H. Whitney Boggs, Shreveport, La.

Pathology of Allergy—A Bridge to Understanding Clinical Allergy
Dr. Bernhard Steinberg, Toledo, Ohio
Discussion opened by Dr. L. O. Dutton, El Paso, Texas

Evaluation of Aerosol in the Treatment of Asthmatic Bronchitis
Dr. Boen Swinney, San Antonio, Texas
Discussion opened by Dr. Narcisse Thilberge, New Orleans, La.

Luncheon—12:30 P.M.
Washington-Youree Hotel, Zephyr Room

Afternoon Session—1:30 P.M.

Round Table—Nutritional Problems in Allergy*
Leader: Dr. Robert Stone, Birmingham, Ala.
Co-ordinator: Dr. Herbert Rinkel, Kansas City, Mo.
Greetings
Clyde E. Fant, Mayor, City of Shreveport
Dr. C. Webb representing the Shreveport Medical Society
Round Table—Dermatological Allergy*
Chairman: Dr. Dudley Youman, Shreveport, La.
I. Where is Allergy Indicated in Dermatology? Dr. Dudley Youman, Shreveport, La.
II. Non-contact Causes of Allergic Dermatitis. Dr. Maurice C. Barnes, Waco, Texas
III. Contact Dermatitis
(A) Plant Oils. Dr. Geo. T. Seibold, Houston, Texas
(B) Cosmetics, Dyes and Drugs. Dr. Ellis P. Cope, Little Rock, Arkansas
(C) Preparation of Poison Ivy Extracts. Dr. Lawrence Halpin, Cedar Rapids, Iowa
Rationalization in Allergy
Dr. J. Harvey Black, Dallas, Texas

Evening Cocktail Party and Banquet

Cocktail Party—6:00 P.M.

Washington-Youree Hotel—Mezzanine Floor

Banquet—7:00 P.M.

Vitamin Deficiencies—Emphasis on Recent Developments
Guest Speaker: Dr. Robert Stone, Nutrition Clinic, Hillman Hospital, Birmingham, Alabama
The Symphony of the Seasons
A Color Rhapsody of Winter, Spring, Summer, Autumn
Dr. Herbert J. Rinkel, Kansas City, Mo.

TUESDAY, APRIL 1, 1947

Morning Session—9:00 A. M.

Aerobiology: Evaluation of Air-borne Allergens
Mr. O. C. Durham, Chicago, Illinois
Discussion: Mr. H. L. Graham, Dallas, Texas
Follow-up Reports on Previous Papers
Dr. F. R. Rugeley, Wharton, Texas
Dr. Paul T. Petit, Beaumont, Texas
Round Table—Treatment of Hay Fever
Chairman: Dr. Bernard G. Efron, New Orleans, La.
Leaders: Dr. Mary Hewitt Loveless, New York City; Dr. French K. Hansel, St. Louis, Mo.; Dr. Oscar Swineford, Charlottesville, Va.
Co-ordinator: Dr. Francis M. Rackemann, Boston, Mass.

Luncheon—12:30 P.M.

Washington-Youree Hotel, Zephyr Room

Afternoon Session—1:30 P.M.

Open Forum—Evaluation of New Drugs in Allergy*
Leader: Dr. Joe S. Shavin, Shreveport, La.
Allergy in Relation to Cardiovascular Problems
Dr. Tinsley R. Harrison, Dallas, Texas
Discussion opened by Dr. Sim Husley, Fort Worth, Texas
The Classification of Asthma
Dr. Francis M. Rackemann, Boston, Mass.
Discussion opened by Dr. Alan Cazort, Little Rock, Arkansas
Allergic Problems in Children
Dr. Jerome Glaser, Rochester, New York
Discussion opened by Dr. Ralph Bowen, Houston, Texas
Business Session—Southwest Allergy Forum

*What is your opinion? What are YOUR PROBLEMS? COME PREPARED TO DISCUSS.

NEW YORK ACADEMY OF SCIENCE

Tentative Program—Friday, April 25

1. Experimental Anaphylaxis in Lower Animals
   Beatrice Seegal
2. Allergic Disease in Lower Animals
   (Classification of Allergic Diseases)
   Lester A. Reddin
3. Serum Sickness
   Samuel Karelitz
   Discussion: Bela Schick
4. Contact Allergy (Epidermal)
   Max Grolnick
5. (a) Allergy of Infection (Relation to Immunity)
   Beatrice Seegal
   (b) Allergy of Infection (Fungi and Fungous Products)
   Marion B. Sulzberger
6. Atopic Allergy (Reaginic sensitivity)
   Matthew Walzer
   Discussion: Stuart Mudd, Sanford B. Hooker
7. Familial Nonreaginic Allergy
   Milo G. Meyer
8. Familial Nonreaginic Allergy as a Predisposing Cause of Common Cold
   Arthur P. Locke
9. The Anti-allergic Action of Sympathectomy
   Arthur F. Coca

* * *

Dr. Stephan Epstein is now Clinical Associate Professor of Dermatology and Syphilology at the University of Minnesota.

* * *

William H. Horwitz, M.D., announces his release from military service and the opening of an office at 412 Beacon Street, Boston, Massachusetts.

* * *

Dr. Frank F. Furstenberg and Dr. Nachman Davidson announce their association for the practice of allergy at 401 Medical Arts Building, Baltimore 1, Maryland.

* * *

Dr. George A. Dean has recently been released from military service and announces his return to private practice at 11 West Church Street, Fairport, New York.

* * *

"Academy News and Notes" published by the American Academy of Pediatrics shows in its treasury report that $17,348.52 was spent for postwar planning.

* * *

Clifford H. Kalb, M.D., announces the opening of his office, Suite 4115 Plankinton Building, 161 W. Wisconsin Avenue, Milwaukee 3, Wisconsin. His practice is limited to clinical allergy.

* * *

Sylvia Ruby, M.D., announces her release from the United States Navy and her return to the practice of allergy at 270 Commonwealth Avenue, Boston, Massachusetts.

NEWS ITEM

Dr. Rollin M. Perkins has returned from military service and has resumed the practice of allergy at his former address, 1005 First National Bank Building, Davenport, Iowa.

* * *

Jack A. Rudolph, M.D., has recently returned from military service and announces his return to practice which is limited exclusively to allergy, asthma, hay fever, hives, and allied allergic conditions. He is located at 350 Lincoln Building, Miami Beach, Florida.

* * *

The annual meeting and twentieth scientific session of the American Heart Association will be held in Atlantic City, New Jersey, on June 6 and 7, 1947. The scientific sessions will take place on June 6 and 7 at the Hotel President which will be headquarters for all meetings.

* * *

Dr. Harold O. Schneider, formerly associated with the Salem Clinic, Salem, Oregon, has now opened his office at 707-708 First National Bank Building, Salem, Oregon. His practice is limited to internal medicine and allergy. He is eager to obtain a trained technician in allergy. Anyone interested please write Doctor Schneider.

* * *

The American Association of Immunologists will hold its thirty-first annual meeting with the Federation of American Societies for Experimental Biology in Chicago on May 19 and 20, 1947. Registration will open at 9:00 a.m. on Sunday, May 18, at the Stevens Hotel. The registration fee will be $3.00. All functions will be centralized in the Stevens and Congress Hotels.

According to an announcement in the January, 1947, issue of *The Journal of Allergy*, 144 new members were elected to the American Academy of Allergy at the third annual meeting in New York City. Of this group fifty-nine (41 per cent) are already members of the College. Of seven members elected to Fellowship, two are also Fellows of the College. The American Academy of Allergy, now representing an amalgamation of the American Association for the Study of Allergy and the Society for the Study of Asthma, has a total of 512 Fellows and members. The American College of Allergists now has a total of 654 members.

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Progress in Allergy

(Continued from Page 88)

86. Swihart, L. F.: Upper respiratory infections in children with special reference to involvement of lymphoid tissue. J. Indiana M.A., 38: 448, 1945.
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BOOK REVIEWS

THE ELECTROCARDIOGRAM—ITS INTERPRETATION AND CLINICAL APPLICATION. By Louis H. Sigler, M.D. 403 pages. 25 chapters. 203 illus. Price, $7.50. New York: Grune and Stratton, 1944.

Because there are many books published on the use and interpretation of the electrocardiogram, only the appearance of such a text profusely illustrating every phase of the subject and containing simple and understandable original schematic drawings is justified. The author, with an extensive consultant practice of twenty years, has made a simplified, comprehensive and thorough analysis of the electrocardiogram and its practical application. There are about 400 electrocardiograms with over 1,400 individual lead strips and original schematic drawings.

Emphasis is placed on the essentials with a broad presentation of the theoretical points and the objective findings.

Separate chapters deal with the frequent and the more unusual cardiac arrhythmias, the tachycardias, the bradycardias, and auriculoventricular and bundle branch block.

The elements of physics and electricity relating to electrocardiography are concisely illustrated in many striking diagrams used by the author for many years when teaching the subject. Trauma of the heart and the six precordial leads are covered unusually adequately.

The cardiologist, as well as the internist, will find this book a useful addition to his library. F.W.W.

THE DIAGNOSIS AND TREATMENT OF BRONCHIAL ASTHMA. By Leslie V. Gay, M.D., with foreword by Warfield T. Longcope, M.D. 119 tables and figures. 334 pages. Price $5.00. Baltimore: Williams & Wilkins Co., 1946.

This book deals with the author's long experience in the field of asthma. The book is of moderate size and necessarily does not attempt to cover all parts of the subject. There are chapters on the physiology of normal respiration and on the etiology, pathology, diagnosis, differential diagnosis, complications, and treatment of asthma.

The chapter on pathology deals with the autopsy findings in twenty-four asthmatic patients. Each case is given in detail, and the tables and conclusions are well done. Special attention, more than usual in books of this size, is used for the psychoso-

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matic aspects of asthma. The author also deals extensively with the use of radium for adenoid tissue, and with other subjects in which he is particularly interested.

One is necessarily struck with the detail into which the author goes in dealing with the rôle of helium and the use of potassium salts, to mention two. Discussion of these relatively unimportant phases of the subject consumes too many pages, pages which could better have been devoted to more information regarding the source of some of the more important causes of bronchial asthma and to a more explicit discussion of avoidance of these allergens, especially house dust.

The author apparently does not think that foods are important and gives little attention to that phase of the subject. Most allergists believe that inhalant allergens are more important causes of asthma than are foods, but almost all feel that foods frequently cause attacks. There is a good section on the relationship of asthma to the nose and sinuses, but many workers in this field are not as surgically minded as is the author.

There are other shortcomings. The index is small and the bibliography meager. Solutions for hyposensitization are given in mixtures without regard to pollen seasons.

A glaring fault is a statement to the effect that scratch tests are inaccurate and that the intracutaneous method should alone be used. Some similarly minded allergists have found to their chagrin that there is no safety in intradermal testing unless these have been preceded by negative scratch tests. Every fatality or near fatality is an indictment of the few who refuse to do scratch tests. Both the scratch and the intradermal methods make for a safer and a more complete diagnostic survey. Swineford *(Journal of Allergy,* 17:24, 1946) is quite correct when he concludes that "every intradermal test should be preceded by the less sensitive scratch test." Any other technique is dangerous. The medical students and physicians who read this book would do well to bear this in mind.

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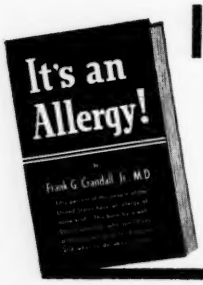

IT'S AN ALLERGY! BY FRANK G. CRANDALL, Jr. M. D.

Just off the press—the most authoritative book ever written for allergic patients. You can recommend this book with confidence because it's by a well known Allergist. It is non-technical and easy for your patients to understand.

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